1   for cardiovascular disease. I have a slide of those

2   specific codes if you would like to see them.

3   DR. RUSKIN: What I'm getting at -- I

4   don't want to waste your time or the committee's time.

5   What I'm getting at is that the definition of

6   cardiovascular disease can be very broad or very

7   narrow.   A broad definition in this situation is not

8   terribly helpful because what you're interested in are

9   the highest risk subsets.

10   Those are patients with left ventricular

11   dysfunction and congestive heart failure primarily.

12   If there is any way that you could help me understand

13   what percentage or what numbers of patients, in fact,

14   had those two diagnoses, it would be helpful. Do you

15   have any LV function data for example?   I wouldn't

16   expect that you would here but I have to ask the

17   question.

18   DR. HOLLISTER: We don't -- none of our

19   protocols nvolved determination of LV function but

20   certainly a number of the patients that entered our

21   protocols had histories of diagnoses, of heart

22   failure, left ventricular dysfunction and the like.

23   We can look at the historical data that was recorded

24   as patients entered into the study and provide that to

25   you.

1   DR. RUSKIN: It would be helpful to look

2 at the QT effects in the subset with congestive heart

3 failure in particular. This may have some importance

4 in treating some of the pneumonias because clearly

5 with the exacerbation of chronic bronchitis, there

6 will be a subset of those patients who have congestive

7 heart failure. It would be interesting to know what

8 the effects are.

9   The last two points are comments. One is

10 that although there was no mean change in QTc effect

11 in the setting of hypokalemia and hypocalcemia five

12 percent, one in 20 of your patients who were

13 hypocalcemic, had developed QTc prolongation of

14 greater than 60 milliseconds which is, I think,

15 important to emphasize and what you would expect with

16 an Ikr blocker and not trivial.

17   The last comment relates to the proposed

18 labeling which you read which surprised me a little

19 bit. I would just like to read it back to you and get

20 your comments.

21   The last sentence says, "Consequently

22 moxi. should be used with caution in patients with

23 congenital   or   acquired   syndromes   of   QTc

24 prolongation..." and I underscore congenital or

25 acquired "...or in patients taking concomitant

1 medications known to prolong the QTc interval Class IA

2 and Class III antiarrhythmics."

3 And you followed it with a statement that,

4 "We found no evidence of risk in these patient

5 populations." I would suggest that you haven't

6 studied those patient populations. That, I think, is

7 the core of this issue, and that is that the highest

8 risk patients are patients about whom we have no data

9 here. You have no information.

10 I didn't see one patient in this database

11 who had congenital long QT syndrome. You've got three

12 in the entire database who were exposed to Class III

13 antiarrhythmic agents. That's just a fact of life.

14 That's the nature of the patient population in

15 conjunction with the constraints that you set on the

16 protocol.

17 We need to, I think, restrain our

18 comments, or at least confine our comments to the

19 database that exists and you don't have the data to

20 make that statement.

21 DR. HOLLISTER: I meant to be sure to say

22 that with the limits of our database we found no

23 effect in those admittedly small numbers of patients.

24 Again, they are **small** numbers.

25 DR. RUSKIN: You have no database there.

1 You have no database. You don't have a single patient

2 with long QT syndrome. You have three patients on

3 antiarrhythmic agents. There is no database on that

4 subset. This is a beautifully worked up drug. You

5 deserve to be congratulated. I think you've done a

6 wonderful job of evaluating it. The comments, I

7 think, that you make should be confined to the data

8 that you have, not data that you don't have.

9   DR. HOLLISTER: I agree.

10   DR. RELLER: Dr. Battinelli.

11   DR. BATTINELLI: I just wanted to as a

12 practicing clinician in some ways amplify what Dr.

13 Ruskin said and point out another piece of -- another

14 problem with that data on the 61 patients. I would be

15 concerned about patients on a variety of medications

16 as most of my patients are. I would agree with some

17 of the others that we're not going to measure the QTc

18 on every single person who comes in for an upper or

19 lower respiratory tract infection.

20   Dr. Ruskin was concerned that there were

21 only three patients on Class III agents. If you look

22 at the drugs that you listed, you listed over 33 drugs

23 and only had an N of 61. There was no patient there

24 on more than one or two at best. I would be concerned

25 with other drugs that are commonly used for long

1   periods of time such as cisapride and some of the

2   others.

3   DR. HOLLISTER: I agree. The numbers

4   often times were one or maybe two in an individual

5   patient. The number of individuals with those drugs

6   was small.

7   DR. RELLER: Dr. Rodvold.

8   DR. RODVOLD: To follow-up with their

9   comments, did you change your protocols to exclude

10   people with cardiovascular diseases or any type of

11   diseases associated with arrhythmias after you found

12   this in your Phase I work?

13   DR. HOLLISTER: No, we did not. The

14   exclusions were for the antiarrhythmic drugs.

15   DR. RODVOLD: But any cardiovascular

16   disease anyone had, they could enroll?

17   DR. HOLLISTER: That's correct.

18   DR. RELLER: Dr. Christie.

19   DR. CHRISTIE: I have a question in Dr.

20   Church's detail. She indicated that six patients who

21   were treatedwithmoxifloxacin had atrial fibrillation

22   versus none of the controls. I just wondered what

23   happened to those patients? What were the clinical

24   outcomes? If she could tell us more about those six

25   patients, please.

1   DR. HOLLISTER: Okay. I have information

2   on those patients. In the largest database we had a

3   total of 13 patients experienced atrial fibrillation

4   either during therapy or within 30 days after therapy

5   with moxifloxacin.   That is in contrast to two

6   patients that we identified in the comparator drugs.

7   Of those eight patients that experienced

8   atrial fibrillation during therapy, and we define that

9   as up to 24 hours after termination of the last dose

10   of moxifloxacin, six of them had histories of atrial

11   fibrillation.   Four of them were on antiarrhythmic

12   drugs that are commonly used for atrial fibrillation.

13   There were no adverse events associated with those.

14   DR. RELLER: Dr. Platt.

15   DR. PLATT: I'd like to ask you two

16   questions about the concentration effects on QTc.

17   Also about the outliers.   First you said that on

18   average the QTc prolongation was six milliseconds plus

19   or minus 26. That's a standard deviation. Would it

20   also be fair to say that something on the order or two

21   or two and a half percent of people exposed to the

22   drug   have   QTc   prolongations   greater   than   60

23   milliseconds? Am I understanding that data correctly?

24   DR. HOLLISTER: The number for our all-

25   paired data set were 10 subjects had QT prolongations

1 | more than 60 milliseconds on moxifloxacin 400.

2 | DR. PLATT: Well, there's another slide

3 | you showed that it was something like 1.7 percent, I

4 | think, had --

5 | DR. HOLLISTER: Yeah, 10 divided by 787 is

6 | about 1.3 or 1.2.

7 | DR. PLATT: Which is consonant with that

8 | standard deviation you showed; that is, among all

9 | comers a couple of percent might have those

10 | prolongations that are above the 60 millisecond cutoff

11 | for whatever 60 milliseconds is worth. I just want to

12 | make sure I'm understanding properly what you're

13 | saying.

14 | DR. HOLLISTER: Yes, that's true. It

15 | might be useful to ask what's the comparable

16 | percentage for those comparator drugs because in that

17 | same slide it looked as though it was a four to one

18 | excess with prolongations of 60 milliseconds or more.

19 | DR. PLATT: That takes me into my question

20 | about concentration effects. That regression line you

21 | put up, if I squint at it properly, it looks as

22 | thought at the upper end there was maybe a 20

23 | millisecond increase in the fitted line. Was I

24 | reading that properly?

25 | DR. HOLLISTER: No. Perhaps better than

1 just looking at the QT would be the delta QT so that

2 you've got in-patient comparisons because that's what

3 the delta of six milliseconds is.

4   DR. PLATT: Right. Well, in the briefing

5 documents we were sent, there was actually a graph

6 that showed delta QTc and it looked not unlike that

7 regression line you showed but it did have -- it

8 looked as though it was pointing to 20 milliseconds at

9 concentrations of 4,000 to 5,000 micrograms.

10   I'm going toward this same question. If

11 4,000 to 5,000 micrograms per mil. is the steady state

12 concentration expected by the end of a treatment

13 regimen, is that --

14   DR. HOLLISTER: The Cmax.

15   DR. PLATT : Right. What proportion of

16 individuals -- putting that data together, what

17 proportion of individuals who have concentrations of

18 4,000 to 5,000 micrograms would be expected to have a

19 delta QTc of 60 milliseconds or more? Can you predict

20 that from the data that you have?

21   DR. HOLLISTER: Only in a way, I think.

22 You know, we tried to obtain the EKGs at or near the

23 Cmax concentration. That range was broad in the

24 database so I can't say that every one was obtained

25 there. In the database in which we were attempting to

1 obtain a Cmax EKG, the mean change was six

2 milliseconds. In the more tightly controlled Phase I

3 studies, you see the regression line there. Maybe I

4 should show the delta QT because there may be some

5 very interesting biology on that.

6 Jim, maybe you can help me find the delta

7 QTc change.

8 Because it's interesting that at very low

9 concentrations of drug it's negative so that when

10 you're at or around the therapeutic --

11 Okay. Renée, that's slide No. 45 on

12 carousel five.

13 At around the what we think are the Cmax

14 concentrations that are going to be achieved with

15 steady state, the slope actually is for delta right in

16 the range that we found it with the Phase III

17 database.

18 Here I showed you earlier the QTc. This

19 is the delta QTc. Here's the zero time point and out

20 this direction here with milligrams per liter of the

21 drug concentration. Again, a lot of scatter in the

22 data. Most of our Cmaxes are going to be falling in

23 this range of the data. You know, as well as this

24 regression line can predict what the change is with

25 all the variability that you see in the scatter there,

1 our finding with the large database was it was around

2 six.

3 DR. PLATT: Just one more comment and then

4 I'll relinquish the microphone. It seems to me that

5 these data are quite consistent with the clinical data

6 you showed but show the tyranny of small numbers.

7 That is, if you plotted the 95 percent confidence

8 intervals around the upper range of doses, what

9 proportion of people would have delta QTc that are in

10 the range that could be worrisome?

11 It's likely that if you treat a lot of

12 people, you'll have a small fraction which is a

13 substantial number in that four to five range. For

14 those who are more than one or two standard deviations

15 above, that still may be a lot of people. It would be

16 useful to know how many that is and what kind of QTc

17 prolongations you could expect for them.

18 DR. HOLLISTER: The numbers that we have

19 from the all-paired valid EKG database are 10 of 787

20 met that criteria of being greater than 60

21 milliseconds prolonged. That might give you the

22 proportion of people that might be above this number

23 at therapeutic concentrations of the drug.

24 We have our largest database with

25 consequent problems in terms of the EKG

1 interpretation.   That number is about 23 out of the

2 1,200 patients meet that criteria, but the noise is

3 much larger in the comparator group, too, so they come

4 up a great deal also.

5   I think your earlier point about these are

6 variable measures and it's hard to ascribe huge

7 effects to measure that has a variability that's four

8 to five times the measure.

9   DR. RELLER: Dr. Murray.

10   DR. MURRAY: Just one. You made a comment

11 that this had not been studied for prolonged periods

12 of time.   Do you have any reason to suspect that

13 prolonged   administration   would   lead   somehow

14 cumulatively to an effect on the QT?

15   The reason I ask is because there is a

16 tendency once the drug is out there on the market to

17 use it for a number of nonapproved indications.   One

18 I can think of immediately is osteomyelitis with a

19 staphylococcus where fluoroquinolone might be used for

20 prolonged therapy.   One would theoretically think of

21 using the most active in vitro one on the market since

22 few have been studied for osteo.

23   Do you have any sort of information on

24 prolonged therapy or would this need to be addressed

25 in the labeling?

1   DR. HOLLISTER: Obviously we're not going

2   for that kind of labeling or those indications. We do

3   have very limited numbers of patients that have been

4   studied for more than 12 days, I believe, in our

5   database. In terms of the effect on QT, we don't have

6   data. All I can say as a clinical pharmacologist is

7   we don't have those issues of drug accumulation going

8   on here. If there is a relationship between drug

9   concentration and the effect on QT, then the maximum

10   effect that we get is unlikely to be any worse.

11   Another way of approach that would be some

12   of   our   Phase   I   trials   where   we   did   acute

13   administration and then chronic administration of the

14   drug. On average the change in QT reduced slightly

15   with chronic administration but those were not the

16   length of time that you're talking about for some of

17   these very chronic illnesses.

18   DR. MURRAY: Thank you. And I have not as

19   a question to answer now but perhaps to just let the

20   sponsor know I would be asking it later, or would like

21   it hear it addressed later in the context of -- and

22   some of this may come up in the FDA's presentation --

23   in the context of assessing the strength of efficacy

24   in general for pneumococcus which might allow us to

25   have a sense of the strength of efficacy against

1 resistant organisms.

2 I would be interested in a review, perhaps

3 in the afternoon or in the question/answer session

4 then, the total number of pneumococci in the CAP

5 studies and how many of those were bacteremic. And an

6 assessment of the severity of the illness of people

7 that were treated with moxifloxacin broken out, in

8 fact, in terms of penicillin resistance and

9 intermediate much as we heard yesterday.

10 I don't expect you to throw that out now

11 but it would be something that -- and some of it may

12 come out in the FDA presentation.

13 DR. HOLLISTER: I believe Dr. Meyerhoff

14 will have some information on that.   We have

15 additional information that we can provide you on that

16 in the afternoon.

17 DR. RELLER: Dr. Christie.

18 DR. CHRISTIE: This drug was not tested in

19 children but once it is approved, it will be used in

20 children.   MY concern was would you expect any

21 cardiovascular problems or any problems in children

22 once the drug is approved?

23 DR. HOLLISTER: Well, you are correct that

24 the drug has not been studied in children.   We have

25 toxicological data in young animals that indicate that

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1 it shares with many of the other fluoroquinolones,

2 some of the effects on joints that are found with

3 other fluoroquinolones and represent a relative

4 contraindication. With respect to the cardiovascular

5 effects or EKG effects, QT effects, we have no

6 information.

7 　　　　　　　　　DR. CHRISTIE: What can we do about that?

8 　　　　　　　　　MR. CALCAGNI: In accordance with the

9 pediatric regulations, we'll have further discussions

10 with the FDA. There are requirements as of April of

11 this year to certainly study any drug that potentially

12 will be used in children. It was not indicated for

13 children and we're not requesting it, but consistent

14 and in the spirit of evaluating drugs, we will be

15 looking at it. We can't put it in our labeling

16 because we did not study it at this time.

17 　　　　　　　　　DR. RELLER: Dr. Parsonnet.

18 　　　　　　　　　DR. PARSONNET: I have a few questions

19 very much related to what Dr. Platt had asked. It

20 relates to some of the outliers. You had it looks to

21 me a difference in the number of outliers, at least by

22 the CPMP criteria that you talked about, the greater

23 than 500 milliseconds and the greater than 60

24 millisecond change. I was wondering in those two

25 categories you had 10 in one and three in the other.

1   There were three who had longer than 500 milliseconds

2   and 10 in the other group. Whether they were the same

3   people, the total was 13?

4   DR. HOLLISTER: Yes. Those categories are

5   nonexclusive categories so, in fact, someone who met

6   a criterion to be greater than 500 milliseconds often

7   times met one of those other criteria, either greater

8   than 60 or greater than 30 to an abnormal value.

9   DR. PARSONNET: Well, that's what I'm

10 asking. I'm asking was that the case. How many of

11 those three were also in that group of 10?

12   DR. HOLLISTER: I would have to look at

13 the data. I can't answer right off the top of my

14 head.

15   DR. PARSONNET: And I guess that then

16 comes to the question that I have which is it seems to

17 me to some degree looking at your dose response, that

18 regression curve that you did, that there is some

19 degree of idiosyncracy to the prolongation of the QT.

20   Some of your people in your very low

21 categories had very prolonged QTs and that this may

22 not be in this respect having a sort of -- and also

23 it's not clear to me that this is a normally

24 distributed variable. That there aren't some people

25 that your means don't reflect, that most people don't

1 change at all but some people change a lot.

2 I was wondering whether -- and this is a

3 question as well for my consultants -- whether, No. 1,

4 the data of QT prolongation are normally distributed

5 and, No. 2, what we are really interested in is the

6 proportion of people who are those outliers as opposed

7 to this mean difference which really to a clinician

8 may be really have much meaning.

9 DR. HOLLISTER: We analyzed our data both

10 in terms of the mean change in QT as well as frequency

11 of outliers and all those data are available to you.

12 I believe Dr. Morganroth can comment about the

13 distribution of QT prolongation and it's variable.

14 DR. MORGANROTH: The small change in a

15 mean QTc duration is not terribly meaningful to

16 clinicians, just as you say, particularly when you're

17 dealing with numbers in the one to 10 millisecond

18 range which are not clinically easy to measure and

19 generally are not measured to that specificity.

20 But when you see in a drug development

21 program in several hundred to 1,000 plus patients a

22 small three millisecond, six millisecond change in

23 QTc, the real question, I think, is whether it's real

24 or not or whether it is -- is it really an effect on

25 cardiac repolarization. That's where one goes back to

1   look at some of the preclinical potassium channel

2   information that might be useful.

3   Also to look at the outliers analysis

4   because, in fact, if the drug is inducing a QT change

5   and the QT change is not spontaneous variability,

6   which is what accounts for most of that distribution

7   you see on the concentration QTc graph in which we

8   don't believe the data are normally distributed for

9   that reason, then the outlier percentages are a guide,

10   if you will, as to the likelihood that, in fact, the

11   drug is causing a QT change versus that it's not when

12   you are dealing with very small millisecond change.

13   I look at the data somewhat differently

14   than it's been presented by Dr. Hollister. When I see

15   a 60 millisecond category in which you have 1.3

16   percent of the drug under consideration meeting that

17   criteria in .3 percent of the "control" group, in this

18   case comparators rather than placebo, while that is

19   statistically probably not different, to me it's

20   meaningful in the sense that there is a difference

21   numerically that is used as a supportive mechanism

22   with IK channel data to suggest that a six millisecond

23   effect is real meaning it's more likely real than not

24   meaning it's more likely caused by the drug or not.

25   As someone over here suggested, the other

1 way that I look at it is what percentage of patients

2 being treated by the drug are going to have a change

3 in the QTc that's more likely due to the drug than

4 spontaneous variability. I think the answer for this

5 drug, and for many drugs of this nature, is in the two

6 to three percent range of patients, which is somewhat

7 comforting because that suggests that 97½ percent of

8 the patients are not going to have it.

9   The other issue which is very important is

10 concomitant drug medication that prolong the QT. In

11 the database of this nature, and frankly in almost all

12 the databases, there isn't sufficient numbers of

13 patients on cisapride or amiodarone or sotalol to

14 really come to any data driven conclusion, it becomes

15 an issue of wobbling in caution.

16   Just like the pediatric issue. We don't

17 have data on pediatrics but we still have to do

18 something or say something about it. I think the same

19 thing holds here. Does that answer you question?

20   DR. PARSONNET: It answers my question

21 somewhat but my concern still is that actually I think

22 that 1.3 percent versus .3 percent may be

23 statistically significantly different.   I also am

24 concerned that the way this is being presented,

25 especially in the way that you are proposing in the

1 labeling, is not as informative to the physicians

2 using it than actually providing that percentage of

3 people who have a dangerously -- what is considered to

4 be a potentially dangerous prolongation of QT.

5 DR. MORGANROTH: The only comment I would

6 make is to say that having a 60 millisecond change

7 shouldn't be looked at as necessarily a dangerous

8 level. It's a level picked by CPMP to suggest that

9 it's due to the drug versus spontaneous variability.

10 Remember, normal healthy persons can have a 75

11 millisecond change over the day.

12 The really salutary effect is that this

13 drug is only going to be used for five or 10 days.

14 You take an antihistamine and it might be used for

15 weeks or months or other drugs that may be used for

16 years. Then a 60 millisecond change chronically which

17 may be, of course, more or less depending on the time

18 of day, would be much more important. I think that's

19 another factor you should consider.

20 But I agree with you. I think that it's

21 important to know the percentage of patients that

22 reach certain criteria and what the likelihood that

23 the drug is, in fact, causing the QT rather than not

24 at all affecting the QT because just a six millisecond

25 change is something that most clinicians would think

1   is ridiculously trivial. In this case I think it's an

2   effect that needs to be understood so that concomitant

3   medication use can be appropriately guided.

4   DR. RELLER: Dr. Ruskin.

5   DR. RUSKIN: I would agree with those

6   comments and perhaps state it a little differently.

7   That is, a small change in mean QT is very difficult

8   to interpret.   The outliers are really the only

9   subsets of interest. What is critical about looking

10   at an agent that you think may affect the QT is what

11   its ion channel profile is. What you know about this

12   drug is that it's an Ikr blocker and that it is both

13   dose and concentration dependent.   Those are very

14   important properties.

15   The effects appear to be relatively small

16   but the fact is it's an Ikr blocker.   A weak Ikr

17   blocker will not cause a problem in the vast majority

18   of patients to whom it's given.   The only patients in

19   whom we have concerns are high-risk subsets.   Those

20   are patients who have what Dan Roden has called

21   reduced repolarization reserve.

22   That is, people with ion channel

23   genetically based ion channel abnormalities that

24   predispose them to agents that block Ikr to predispose

25   them to problems with ion channel blocking agents; (2)

1   People at particularly high risk, elderly females with

2   structural heart disease; and (3) people on

3   concomitant Ikr blockers for other reasons. Those are

4   the subsets in whom we have no data here.

5   I think that when you make a decision

6   about whether or not you use a drug in large

7   populations of patients, you have to be influenced by

8   the benefits and the risks. If you have a drug that

9   clearly as a favorable profile as this one does, you

10   may decide that the benefits outweigh what is probably

11   a very small risk but you want to be intelligent about

12   how you label it.

13   That was the reason for my comments to Dr.

14   Hollister about the proposed labeling. There is

15   absolutely no data here to suggest that this drug

16   should be used with caution in people with congenial

17   long QT or concomitant QT prolongation. It just

18   shouldn't be used with them period. I think to answer

19   your question, the outliers are the critical subset

20   and they are the subset about whom we have little to

21   no data. That's where the concern lies.

22   You can do a guesstimate of the upper

23   bound if you assume about 60,000 person weeks or --

24   no, 6,000 person weeks of exposure here. The upper 95

25   percent boundary for potential events here is

1 somewhere around five per 100 -- no, five for 10,000.

2 The event rate here could be as high as

3 one in 2,000. It's probably a lot lower than that but

4 you can't exclude the possibility of, say, two events

5 in

6 -- excuse me, one event in 2,000 uses of this drug

7 based on this data in this relatively low-risk subset.

8 That's the problem that you're faces with in grappling

9 with this issue. You've got short duration exposures

10 which is almost a favorable thing but a very limiting

11 feature in terms of assessing risk.

12 DR. RELLER: Dr. Temple.

13 DR. TEMPLE: Can I just ask Jeremy

14 something? In these people who might be at greater

15 risk, is what you would expect to see a larger effect

16 on QT or a different consequence of a given QT effect?

17 For example, we know that people on

18 diuretics are more susceptible to getting torsade from

19 a drug that is capable of causing it. But is that

20 because their QT effect is larger or because they are

21 more susceptible to whatever is there already?

22 DR. RUSKIN: I think it can be both, Bob.

23 I think that clearly you do tend to see longer QTs in

24 people who have other predisposing factors like

25 hypokalemia or other drugs that block Ikr. There are

1   certainly cases of torsade that occur without dramatic

2   QT prolongation so it's not the QT and I think Joel

3   said this, or someone in one of their presentations.

4   It may actually have been Dr. Hollister

5   who said very clearly that the degree of QT

6   prolongation is neither necessary nor sufficient to

7   predict risk. It's a factor but it's certainly not

8   the only factor. YOU can see torsade with even modest

9   degrees of QT prolongation in some patients. Most

10   people who develop drug induced torsade have QTc in

11   the range of 500 or greater but by no means all.

12   DR. TEMPLE: That goes a little to how one

13   might study the interaction. If you have to get an

14   event to learn something, that makes it very

15   difficult. If you simply have to look at the high-

16   risk people and see whether their QT was more

17   prolonged than other people, you could actually study

18   that.

19   DR. RUSKIN: I think it makes it very,

20   very difficult to study. That's why you're left with

21   using some sort of guesstimate of a risk benefit ratio

22   never really getting a tight grip on the risk. You've

23   seen this with the antiarrhythmics that work by

24   prolonging the QT interval and even there we have

25   trouble estimating what the real risks are.

1   DR. RELLER: Dr. Soper.

2   DR. SOPER: As a follow-up to Dr.

3   Christie's question, is this drug safe to give

4   reproductive age group women who may be pregnant but

5   who don't know it? Has there been any inadvertent

6   administration to this drug to a pregnant woman and do

7   you have any outcome data?

8   DR. HOLLISTER: I don't have anything.

9   Dr. Eckhard van Keutz is the toxicologist who is

10   associated with the development of this drug and he

11   can answer that question in terms of the animal.

12   DR. VAN KEUTZ: We have started

13   moxifloxacin in the normal range of reproduction

14   toxicity studies and we have performed studies in rats

15   as well as in monkeys. In none of these animal

16   species we have seen any indication of teratogenicity

17   but we have seen signs of embryo toxicity. This

18   occurred only at dosages which were already maternally

19   toxic.

20   This is certainly not a direct affect of

21   the drug but it's indirect or a secondary affect due

22   to the maternal toxicity. In addition, we have seen

23   in the monkey study, again at a maternally toxic dose,

24   an increased rate of abortions but, again, no

25   teratogenicity.

1   DR. SOPER: You talked about the

2   arthropathy in small children. Can you explain on

3   that a little bit? Or in small animals, I guess.

4   DR. VAN KEUTZ: Okay. We have performed

5   this typical young beagle dog toxicity study and the

6   outcome of this study was that moxifloxacin is a very

7   typical quinolone which means that we have induced

8   these very well known damages to the joints at a dose

9   of 30 milligram per kilogram which caused problems to

10   P concentration and the plasma of approximately eight

11   milligrams per liter.

12   I think at this athrotoxic concentration

13   we are in the range of the other quinolones. There's

14   nothing which has surprised us. For us it would be a

15   surprise to have a quinolone which was not inducing

16   the typical athrotoxicity.

17   DR. RELLER: Dr. Norden.

18   DR. NORDEN: I think we've all -- at least

19   I've learned much more about QT than I ever thought I

20   would know or want to know. I am concerned and Dr.

21   Ruskin has been very helpful. One of the questions I

22   have for the FDA grepafloxacin and sparfloxacin, which

23   are both approved, are listed in the slides as having

24   prolonged QT intervals of the same or slightly longer

25   duration if you just look at the mean.

1   Do we have data on them? I mean, were

2   they studied in the same way or examined? Do we have

3   any experience that would help us in terms of

4   evaluating this quinolone?

5   DR. NORDEN: I think that the comment that

6   was made by Dr. Ruskin with regards to the company's

7   efforts here in terms of studying this phenomena are

8   certainly accurately. I think that, as far as I know,

9   neither sparfloxacin nor grepafloxacin was studied at

10   nearly the same degree of intensity. I think that is

11   obviously an issue that we need to assess once we

12   hopefully, as part of this meeting, get a framework

13   for.

14   You'll notice that one of our last

15   questions to the committee this afternoon is about

16   talking a little more -- and there has already been

17   some discussion about the parameters that are

18   appropriate for anti-infectives and, in truth,

19   probably for noncardiac agents -- to look at and the

20   question will come up about assessing some of these

21   other drugs.

22   There is some information about QT changes

23   on sparfloxacin. I know some was done. We were not

24   involved in that assessment. When I say we meaning

25   current division who is reviewing this product.

1   As far as grepafloxacin, there was some

2   information. You saw the QT prolongation. On the

3   other hand, if I recall correctly, grepafloxacin did

4   not seem to have in the initial data the same exposure

5   prolongation relationship that, for instance, has been

6   seen with this product. That may, in fact, be a

7   little different.

8   I think it's fair to say that what Bayer

9   has done for moxifloxacin probably sets a new standard

10 for the overall evaluation of products, certainly

11 anti-infective products, with QT prolongation. The

12 question is how to sort of use some of this to apply

13 to new products and perhaps at some level to products

14 that are already approved. As was also noted, this QT

15 prolongation is not limited to the fluoroquinolones.

16 There are issues, in particular, with the macrolides

17 that may well also have to be subsequently assessed a

18 little more.

19   DR. KWEDER: I actually have a question

20 for Dr. Hollister. Some of the slides that you've

21 showed looking at the pharmacokinetics of the 400

22 milligram dose, as well as some of the ratios that

23 you've looked at, the Cmax MIC 90 really do show, you

24 know, that fall well above the eight to 10 range for

25 strep. pneumo indicate that you've got a pretty wide

1 margin for expected efficacy.

2 When you take that in combination with the

3 suggestion of a concentration effect that dose matters

4 for risk of QT prolongation, and the fact that you

5 also -- it's interesting that you also have some older

6 studies of the 200 milligram dose that showed some

7 degree of efficacy.

8 When you presented your QT data, it was

9 for all moxi. studies. Do you have any data on QT at

10 the -- even the mean QT which we think may not be the

11 ticket here, but do you have anything that teases out

12 a distinction between that the 200 milligram dose and

13 400 milligram dose?

14 DR. HOLLISTER: I can let Dr. Church

15 comment because the studies that you are referring to

16 or the parameters that you are referring to were part

17 of her presentation. We do have some data at the 200

18 milligram dose level but that dose level was abandoned

19 because in our Phase II trials we didn't think we had

20 adequate efficacy at that concentration.

21 DR. KWEDER: Right. I guess I'm thinking

22 more about the linear pharmacokinetics here.   There

23 appears to be a linear effect of the QT prolongation

24 as well. I'm just wondering if you have any data at

25 any other dose of moxi. other than the 400 milligrams

1 on the QT issue.

2 DR. HOLLISTER: The progression slide that

3 I showed you was our Phase I database where doses

4 ranged from 50 milligrams to 800 milligrams. We've

5 also included in the NDA and the special safety

6 section on QT the IV data plotted in the same fashion

7 indicating that it does look like it's a similar

8 relationship throughout.

9 DR. KWEDER: Right. And I'm just asking

10 about in the other clinical studies, the non Phase I

11 did you have any data? Your mean QT changes come from

12 the clinical trials. Did you have any of that data

13 from the 200 milligrams or were those studies -- I

14 gather that they were already completed by the time

15 you began to look at this issue in the clinical trials

16 beyond the Phase I PK data.

17 DR. HOLLISTER: We do have limited

18 information on the QT effect. In our clinical

19 pharmacology studies we did have a dose group with 200

20 milligrams orally during which we obtained Cmax EKGs

21 and determined the QT interval there.

22 The 37 subjects that were in that trial

23 had a mean change of 4 plus or minus 18 so it was

24 less. I think it's probably better yet, though, to

25 sort of use the regression because that more directly

1 relates the drug concentration with the effect on QT.

2 DR. RELLER: Dr. Danner.

3 DR. DANNER: Do you have data on how this

4 drug affects potassium and magnesium excretion from

5 the kidney? The second question, in terms of the

6 accumulation of this drug in tissues, over what time

7 period does that occur? What is the half life in

8 tissues? Is it likely if people use the drug for

9 longer periods of time that the drug would continue to

10 accumulate and levels would continue to rise in

11 tissues?

12 DR. HOLLISTER: We do have some tissue

13 accumulation studies in Phase I and Phase II and in

14 small numbers of patients multiple time points. We

15 also have a dialysis and skeletal muscle study. Most

16 of those studies, however, were done with a single

17 dose administration of very short term.

18 There is, as Dr. Church showed you,

19 considerable accumulation in pulmonary tissues which

20 is helpful in this sort of setting. Our data for

21 skeletal muscle is that the concentrations reached in

22 skeletal muscle are about 80 percent of the plasma

23 concentrations of the drug.

24 We don't have data to address the

25 possibility of long-term accumulation in tissues but

1 for skeletal muscle the ratios are less than plasma

2 concentrations.

3   We do have from clinical pharmacology Dr.

4 John Lettieri who can also comment on some of those

5 data.

6   DR. LETTIERI: I'll just make the comment

7 that, in fact, the half life from tissue is the same

8 as the parent drug, about 12 hours, so there wouldn't

9 be accumulation beyond what you see with the single

10 dose.

11   DR. RELLER: We're running short on time.

12 We wil big up some with a slightly reduced lunch

13 hour. I would like to close this portion of it before

14 the break with one final query because it directly

15 relates to the sponsor's presentation and proposals.

16   Dr. Hollister, given the limits of

17 interpretation that have been expressed of the

18 clinical importance of the mean QTc prolongation in a

19 general population as opposed to a subset, could you

20 share the sponsor's rationale for proposing the

21 comparison and the proposed QT labeling, the

22 comparison with a single comparator agent,

23 clarithromycin. What was the thinking there?

24   DR. HOLLISTER: The inclusion of

25 clarithromycin was because that was used in the larger

1   scale studies as the comparator drug.

2   DR. RELLER: Thank you. We will break for

3   15 minutes and then reconvene.

4   (Whereupon, at 11:00 a.m. off the record

5   until 11:16 a.m.1

6   DR. RELLER: I'd like to ask everybody to

7   take their seats so that we can begin the next portion

8   of our -- the last portion of our morning session. As

9   always happens on the second day of a two-day meeting,

10   there are those who must meet flights before the final

11   hour and we want to have ample time for fair

12   discussion and to address the specific questions asked

13   of the advisory committee by the FDA.

14   I would like now to ask Dr. Robert Temple

15   to initiate the FDA presentation.

16   DR. TEMPLE: Thank you and good morning.

17   It's still morning. How's that? Okay. That's okay.

18   I'll just use this. I don't have any slides today and

19   I would be surprised if I can tell you anything that

20   Dr. Ruskin and others cannot but let me talk a little

21   bit about QT prolongation and what it means to us.

22   QT prolongation and the ability of drugs

23   to do that, to cause torsade and sudden death, is

24   clearly one of the most important adverse consequences

25   of drugs. It has lead to withdrawal of some therapies

1   and severe limitations of use.

2   It's a relatively new bad effect of drugs.

3   Wasn't really recognized, to my best knowledge, until

4   about 1982 when we encountered a calcium channel

5   blocker called lidoflazine.   We were very close to

6   approving it when I ran into an English antiarrhythmic

7   specialist named Dennis Krickler at a meeting and

8   mentioned the drug and he said, "Oh, kills people,

9   doesn't it?"

10   Whereupon, we looked and found in the

11   literature plentiful evidence that at least in people

12   who had recently been converted from atrial

13   fibrillation it caused plenty of nasty arrhythmias.

14   Actually, the arrhythmias were published in the

15   journal article and were obviously torsade, although,

16   as far as I know, it wasn't named yet.   There they

17   were.   Even an amateur could recognize them.

18   It's clearly a growth industry. Since the

19   early day of lidoflazine and sotalol and things like

20   that we've discovered dozens and dozens of drugs that

21   have at least some property of this kind which has

22   made everybody extremely nervous because it isn't

23   clear what to do about this phenomena.

24   Drugs with the capacity to block

25   appropriate channels and cause QT prolongation show up

1 in every drug class. Terfenadine and astemazole are

2 antihistamines with major effects depending on the

3 dose and depending on whether you interfere with their

4 metabolism.

5 Thioridazine, sertindol, pimozide, other

6 antipsychotics seem to have some effects of this kind.

7 Type III antiarrhythmics do, of course, by definition

8 because that's what they do. Some of those effects

9 are very large. Nonetheless, some of those drugs are

10 used usually to treat bad arrhythmias.

11 Calcium channel blockers sometimes have

12 this property. Lidoflazine did. Bepridil does. As

13 a consequence, it's reserved for people whose angina

14 doesn't respond to anything else. There was once a

15 drug in Europe called prenylamine which was one of the

16 first drugs every discovered with this property, sort

17 of a landmark drug.

18 Drugs that alter GI motility like

19 cisapride and domperidone have QT activities.

20 Ketanserin is an anti-hypertensive serotonin

21 antagonist. The list goes on and on. I'm not sure

22 everything on the list that Joel found is real but

23 there are candidates in every category.

24 From a regulator's point of view, it's

25 very difficult to know what to do with these. The

1 poles of view, I would say, are that once you discover

2 this property, you are really in trouble. That's one

3 because it's hard to know how to quantify the risk.

4 The other pole would be dose matters, concentration

5 matters, size of the effect matters. It's hard to

6 know where to come out in these because the experience

7 isn't good enough on the cases that are difficult.

8 What is also obvious is that what the drug is for

9 always matters and how good it is always matters.

10 I should say it's not clear to me, maybe

11 people here can say, whether we should be looking at

12 corrected QT or QT. All the bad actors I know affect

13 both. I have never understood the logic of thinking

14 that corrected QT is the better measure. The reason

15 for correcting QTs are historical and arose long

16 before anybodybeganthinking about blocking potassium

17 currents.

18 The clearly bad actors, I think it's fair

19 to say, all prolong both QT and QTc and have pretty

20 good sized effects when you look at mean effects, in

21 the neighborhood of 20 milliseconds or so. Now, that

22 may be what they do by themselves or it may be what

23 they do when you inhibit their metabolism so that the

24 concentration goes up.

25 The drugs of that kind are drugs like

sotalol and bepridil and other Type III antiarrhythmics. The effects are so prominent with those drugs that you actually see cases of torsade in the NDA database. It's not hard to detect these. If metabolism blockage is required, you won't see those in the NDA database because that probably won't happen.

There is concern that factors other than the absolute size of the QT prolongation matter that susceptibility can be enhanced and that there may be an interaction. How well worked up this is not so clear to me. But we do have several examples. A drug called ketanserin, a serotonin antagonist, was put into a very large study, an outcome mortability study of patients with peripheral vascular disease.

What was discovered was a profound increase in mortality in the patients who happened to be on a diuretic. I don't think, but I'm not sure, that was because their QT was affected more. I believe it's because the consequence of the QT prolongation effect of the ketanserin was more severe. There are other examples in which hypokalemia has triggered events that perhaps were not present without that.

It's also possible that some underlying

1 conditions, as Jeremy said, like congestive heart

2 failure may exaggerate the response to a given

3 increase.   There may be an interaction of patient

4 substrate and the size of the effect and it's very

5 hard to say that's true.

6   As I said, there's a point of view that

7 says that any evidence of QT prolonging effect means

8 that we are going to have major trouble. The reasons

9 for thinking that are several. One is that every drug

10 known to cause torsade which, by definition requires

11 QT prolongation, is also associated with cases of

12 polymorphic ventricular tachycardia which is without

13 QT prolongation.   That makes you wonder what the

14 precise mechanism is.

15   Another   reason   is   the   general

16 philosophical view that those responses for most

17 events are continuous and they don't drop off to

18 nothing usually, although there must be some things

19 with thresholds.

20   It also seems likely, but how well studied

21 this is is not clear to me, that when the drug with a

22 small effect is used with another drug that also has

23 the same effect or is used in people who are unusually

24 susceptible, there will be an interaction so that even

25 a drug with a small effect might cause trouble. I'm

1 not sure how well studied that is but it doesn't seem

2 unlikely.

3   Probably most important is as a number of

4 people discussed and Dr. Platt suggested, it isn't the

5 mean that matters.   It's how you affect the

6 distribution.   It may be that we should start

7 representing QT effects not as means but as either

8 cumulative distributions to see what fraction of

9 people have a change or more than a certain size, or

10 the bell shaped distribution, and then look at what

11 the tails are.

12   It seems likely if the mean is very small,

13 one millisecond or so, you may not be able to see much

14 effect on the tail but that does seem where people

15 should look.   By definition, if you change the

16 meaning, you will probably change it in the

17 distribution.   It seems likely that more people will

18 get into a danger range and that's probably what

19 everybody should focus on.

20   Anyway, those are all reasons for thinking

21 that any effect might be something to worry about. I

22 wouldn't dismiss that but I think there is another

23 point of view that is also supported by some data.

24 It's fairly clearly that there's a dose response

25 relationship in most cases between QT prolongation and

1   dose, or concentration. That would be better. There

2   is some relationship at least between the effect on

3   the QT and how much trouble you get into.

4   The reason can even address that question

5   -- sorry. The problem here is that while QT effects

6   are frequent and easily detected in clinical trials,

7   causing torsade is rare and it's not easy to detect

8   that NDA databases. But there is one advantage we

9   have here. That is that torsade is virtually

10   pathomnemonic of an effect on one or another of the

11   ion channels. It's readily detected as a problem.

12   It's, therefore, rather much as aplastic

13   anemia, agranulocytosis, and things like that are.

14   It's fairly readily attributed to drugs. People

15   notice this and they immediately worry about what drug

16   people are on and then report it to us.

17   So it seems at least likely that you can

18   learn about whether drugs have the ability to cause

19   torsade by looking for torsade in the post-marketing

20   period. It's a relatively favorable one. Sudden

21   death, on the other hand, is extremely difficult

22   because many things cause sudden death but not that

23   many things cause torsade.

24   So the marketing experience with some of

25   these drugs it seems to me matters. Now, we know, for

1 example, for terfenadine, that it's extremely easy to

2 discover. Not that we discovered this rapidly. We

3 should have but now we know more. It's extremely easy

4 to discover that terfenadine taken in combination with

5 a cytochrome P450 3A4 inhibitor causes Torsade de

6 Pointes. There are many, many cases. Hundreds. It's

7 very easy to detect that.

8   We looked also to see whether there were

9 any cases in which there was no 3A4 inhibitor. There

10 may be a debate about whether there are any but there

11 are very few. Perhaps none. That is a drug that has

12 a small QT effect even in the absence of an inhibitor.

13   Our experiencewithastemazole, another QT

14 prolonger, was similar. It was fairly easy to

15 discover clear cut cases when people took more than

16 the 10 milligram recommended dose, but few, if any,

17 cases at the 10 milligram dose. It doesn't really

18 matter whether there was one or two. There were many

19 fewer, even though many more people were exposed to

20 the larger dose again suggesting a dose response.

21   For dofedilide, a drug recently approved

22 to maintain sinus rhythm in people who have been

23 having atrial fibrillation, the frequency of torsade

24 went down when dosage was suggested for renal

25 function. It didn't go to zero but that's a drug

1 whose mechanism is to prolong the QT. The rate went

2 down when the dose was appropriately modified.

3 I've been talking with Jeremy about this

4 but there are a few cases to my knowledge of cisapride

5 induced torsade in the absence of an interfering drug.

6 He thinks he knows of some and he's going to report

7 them from now on. But most of the cases anyway occur

8 when you interfere with its metabolism and send the

9 blood level way up.

10 Domperidone is another motility modifying

11 drug which given intravenously causes torsade while

12 the infusion is still going on. It's really easy to

13 detect but it's been difficult, not necessarily

14 impossible. There's probably some internal debate

15 about it. It's been difficult to conclude that it

16 causes it when you give it orally when the blood level

17 is much lower.

18 This leads me to think that dose and size

19 of response matter to how much of a risk a particular

20 drug is. What isn't clear is where the cutoff point

21 is or if there is one. I would feel happy to say that

22 something with one millisecond mean increase probably

23 is no problem and that something with a 20 millisecond

24 increase probably is a problem. I don't think any of

25 us can tell you where the problem gets very small or

1   disappears.

2   Now, having said that, one wants to be

3   sure one isn't giving more of a drug than one needs

4   to. You are the infectious disease people and need to

5   think about this, but one important question is

6   whether the dose at 400 really is needed in all cases

7   or whether a lower dose would do just as well, at

8   least for some infections, and keep people further

9   away from whatever risk there is. Dose becomes very

10   important.

11   I should tell you where we are as an

12   agency. We don't have a formal policy. We don't even

13   have a policy that we put out and then withdrew like

14   the CPMP does. They are ahead of us but we are

15   thinking actively about this. A joint FDA task force

16   is forming to review all available data -- you learn

17   a lot from history here -- and try to think about what

18   an appropriate clinical and preclinical workup is of

19   these cases and try to define risk as best we can.

20   So far, unfortunately for both us and you,

21   it's kind of case by case and the only way to go is to

22   try to make everybody pay attention and pull together

23   the best expertise we can find.

24   Thank you. Any questions?

25   DR. RELLER: Since we will be returning to

1 this issue after the safety presentation, which I

2 would like to do immediately after lunch so that we

3 can have continuity fusing questions for Dr. Temple

4 after and in concordance with the safety presentation,

5 I've asked Dr. Meyerhoff if she would move her

6 presentation forward before lunch.

7 Then we'll have her presentation and then

8 our lunch break from approximately 12:00 till 1:00

9 starting promptly at 1:00 with the safety presentation

10 by the FDA and then moving as swiftly but judiciously

11 as we can to addressing the questions given the

12 constraints of having sufficient voting members to

13 have a real sense of the entire committee presented

14 for FDA's further consideration.

15 Dr. Meyerhoff. Thank you, Dr. Temple.

16 We'll be back to you in the afternoon.

17 DR. MEYERHOFF: Good morning. Can people

18 hear me? Can people hear me now? Not projecting?

19 Can people hear me now? Okay. Thanks. Thank you.

20 Good morning. I'm going to be presenting

21 the FDA's perspective on clinical efficacy for

22 moxifloxacin.

23 As you've already heard this morning,

24 Bayer is seeking a claim for four different

25 indications on the draft label. Those are acute

bacterial exacerbation of chronic bronchitis, skin and skin structure infections, acute sinusitis, and community acquired pneumonia.

These last two indications are particularly noteworthy because for both of them among the organisms that are sought in the label is penicillin resistant streptococcus pneumoniae. This is a claim that has not previously been granted to any antimicrobial. For those of you who were here yesterday, it is also under discussion for another drug in this class.

I'm going to give an overview of the efficacy data initially by saying a number of pivotal trials have been reviewed for each of these four indications. In general, the FDA's analysis by both intent to treat and for protocol populations generally agrees with that of the sponsor, and that is that clinical efficacy has been demonstrated in the four indications.

I would like to focus my discussion on the claim for clinical efficacy and the treatment of infections caused by pen. resistant pneumococcus. For this purpose I'll focus on the pneumonia and the sinusitis indications.

Let me just make a couple of statements

about language and usage because these terms get long and I think interfere with the flow. In any case, when I'm using the term efficacy simply for the purposes of my talk, I'm referring only to clinical efficacy. Resistance again only refers to penicillin resistance. I think we are all in agreement that the MIC cutoff for that is the current NCCLS criterion which is two micrograms per ml. Similarly, any references to pneumonia refer specifically to community acquired pneumonia.

I would like to start by looking at overall efficacy in the pneumonia by highlighting two representative studies. The first of these is D96026. This was conducted entirely in the United States entirely in outpatients spread over 60 centers.

The control agent in this study was clarithromycin. I would point out that the dose used, 500 milligrams BID, is actually twice the FDA approved dose for pneumonia for clari.

The test of cure visit was undertaken at the late follow-up; that is, 21 to 28 days following completion of therapy. I think you can see from the table I'm showing that both per protocol and intent to treat analyses demonstrate efficacy rates that are equivalent to those observed for the comparator

1 agency. These do meet the statistical criterion for

2 equivalence in that the 95 percent confidence interval

3 around the differences and efficacious rates in both

4 analyses have a lower bound that's greater than minus

5 10.

6 I want to look at a second pneumonia study

7 and that's No. 140. This study was conducted entirely

8 outside the United States at over 80 centers. The

9 comparator agent was amoxicillin, 1,000 milligrams

10 TID. Again, it think it's important to point out that

11 this is twice the FDA label dose for amoxicillin for

12 this type of infection.

13 This study's organization was centered in

14 Europe and the genesis for the choice of this dose is

15 that a number of European countries are now

16 recommending this higher dose of amoxicillin for

17 initial treatment of community acquired pneumonia

18 because of decreasing penicillin susceptibility among

19 clinical isolates of pneumococcus.

20 This study is interesting for a couple of

21 reasons. One is it was actually enriched for patients

22 with pneumococcal infection by requiring some

23 additional entry criteria. Besides patients needing

24 to have evidence of pneumonia, they also needed to

25 have any two of the following five findings; that is

1 disease of rapid onset within 48 hours of

2 presentation; temperature greater than or equal to 39

3 degrees; pleuritic chest pain; frankly lobar

4 infiltrate on chest x-ray; or gram positive cocci on

5 sputum gram stain.

6 Thought this is a study of two oral

7 agents, about 80 percent of the patients were

8 hospitalized. I think we need to realize that's

9 probably a somewhat different situation than we would

10 see in this country. Again, these patients were

11 deemed suitable for oral treatment but a very large

12 proportion of them did go into the hospital. All of

13 them had blood cultures drawn.

14 If we look at the overall efficacy rates

15 in both the per protocol and intent to treat analyses,

16 again I think we can see that equivalence is

17 demonstrated to high dose amoxicillin in both cases.

18 I want to turn now to talk specifically

19 about pneumococcal and resistant pneumococcal

20 infections. I think there are a number of questions

21 we want to ask about moxifloxacin when we start to

22 consider this issue. Firstly, does it work in

23 infections due to penicillin susceptible pneumococci.

24 The first bullet point will be an attempt to address

25 that question.

1   Secondly, what kind of data do we have to

2   tell us something about activity against resistant

3   strains or strains with intermediate susceptibility to

4   penicillin.   Thirdly, what types of supporting data

5   can supplement what we can learn from the clinical

6   trials.

7   There was a detailed discussion of these

8   types of data this morning and I'm going to focus

9   mostly on the first three bullet points for the

10 purposes of my discussion.

11   Drs. Church and Zinner summarized a

12 significant amount of data on in vitro microbiologic

13 studies, animal models, and PKPD ratios that I think

14 attest to the preclinical activity against

15 pneumococcus that has been seen for moxifloxacin.

16   The data submitted in this original NDA

17 are really our first opportunity to assess the

18 clinical efficacy of this drug in gram positive

19 infections.   The pneumonia indication is our first

20 opportunity to see how it does in pneumococcal

21 pneumonia.

22   For the purposes of this particular

23 organism, I would like to turn again to study 0140.

24 Again, this is the study that was enriched for

25 pneumococcal infection and provides us with a

1 significant number of patients who were infected with

2 this organism.

3 Overall, efficacy, which is shown in the

4 first row of this table, again for moxifloxacin and

5 the control agent look to be comparable. The control

6 was high dose amoxicillin for this study. If we look

7 at clinical efficacy in pneumococcal pneumonia across

8 all of the pneumonia studies, a similar point is made.

9 That is, moxifloxacin achieves comparable efficacy

10 rates to the comparator agent. Just to remind you,

11 the comparator is either high dose amoxicillin or

12 clarithromycin in all of these studies.

13 This study, 0140, is an unusual

14 opportunity to gather data on bacteremic patients with

15 pneumococcal pneumonia. It enrolled over 400 and I

16 think gives us a chance to look at this particularly

17 interesting subpopulation.

18 I've chosen to focus on them for two

19 reasons. One is that patients with an infiltrate on

20 chest x-ray who grow pneumococcus from their blood

21 represent the gold standard in diagnostic criteria for

22 pneumococcal pneumonia. Secondly, these are a

23 particularly sick subpopulation of patients with this

24 infection.

25 If you look at the first row of this

1 table, you can see that there are 21 patients who were

2 bacteremic with pneumococcal pneumonia in study 0140.

3 The clinical efficacy rate achieved among those

4 patients treated with moxifloxacin was 70 percent.

5 For those treated with amoxicillin 100 percent. These

6 are small numbers. They are not amenable to a lot of

7 statistical manipulation. I offer them mostly for

8 your inspection.

9   If we look at the second row in this table

10 which is those patients who only had a positive

11 culture from the respiratory tract; that is, not a

12 positive blood culture. Efficacy rates between the

13 two treatment groups appear to be more similar.

14   I would like to point out to those of you

15 who had seen the briefing document that these numbers

16 are slightly different from the table that you have in

17 the briefing package. The reason for that is back

18 before I put the tables in, I learned of a small

19 number of additional patients who were bacteremic and

20 also for the need to reclassify some of those who had

21 positive respiratory cultures.

22   For those of you who haven't seen the

23 briefing package, I don't think these numbers changed

24 things significantly. The breakdown between

25 moxifloxacin and amoxicillin for the bacteremic

1   patients is quite similar as is the comparability of

2   those with positive respiratory tract cultures.

3   Let me give you a little bit of

4   information on the patients who were bacteremic.

5   After Dr. Murray asked the question a little earlier

6   this morning, I have tried to separate this out. Of

7   the 21 patients who had pneumococcus grow from their

a   blood in this study, we had MIC data on 18. Eight of

9   those patients received moxifloxacin and 10 received

10   amoxicillin. This is only my recollection and I

11   believe it's correct but I'm not 100 percent sure. I

12   would ask anyone at Bayer if they can remember those

13   line listings better than I can.

14   I think the eight moxifloxacin bacteremic

15   patients all had pneumococcal isolates that were

16   susceptible to penicillin. The 10 patients who

17   received amoxicillin who were bacteremic had two

18   patients infected with resistant isolates.

19   I'll give you a little bit of clinical

20   information on the three patients treated with

21   moxifloxacin who were clinical failures. These were

22   all men. Their ages were 55, 75, and 85. The MICs of

23   their isolates ranged between .016 and .032. Two of

24   the patients had underlying congestive heart failure.

25   One of them developed an empyema on day six of

1   therapy.

2   Let's stick with study 0140 to start our

3   discussion of efficacy in resistant pneumococcal

4   pneumonia. There were a very small number of isolates

5   for us to look at in this study. There were nine

6   total, six in the group treated with moxifloxacin,

7   three in the amoxicillin group.

8   Again, I think we can see there is a

9   divergence in efficacy rates in this small number of

10   patients with the 67 percent cure rate being the key

11   in the moxifloxacin group and 100 percent cure in the

12   three patients who received amoxicillin.

13   Of the six penicillin resistant isolates

14   from the moxifloxacin treated patients, five of them

15   had MIC values of 2.0. One had an MIC of eight. Of

16   the three penicillin resistant isolates from the

17   patients treated with amoxicillin, two were

18   bacteremic.

19   I'll give you a little bit of clinical

20   background on the two moxifloxacin failures. The

21   first, a 67-year-old woman with a history of chronic

22   bronchitis whose pneumococcal isolate had an MIC of

23   two. This woman took a full course of therapy but was

24   observed to relapse eight days following completion.

25   She was considered a cure after treatment with

1 augmentin.

2 The second patient was a 38-year-old man,

3 also with a history of chronic bronchitis. His

4 isolate had an MIC of eight. He was discontinued from

5 the study after six days for an insufficient

6 therapeutic effect and was switched to treatment with

7 IV cefataxime.

8 This is a limited amount of data but at

9 this point it's not possible to conclude that

10 moxifloxacin is the clinical equivalent of high doses

11 of amoxicillin for the treatment of resistant

12 pneumococcal pneumonia.

13 I think the next thing we want to ask

14 ourselves is there a way to learn more about the

15 efficacy of moxifloxacin in this special subpopulation

16 of patients. We had very small numbers from study

17 0140. For those of you who may have been following

18 this issue over the past year, there have been a

19 number of public and private discussions with industry

20 about development of agents for resistant pathogens

21 and the paucity of resistant clinical isolates when

22 people actually go out and try to study them.

23 In the course of these discussions, the

24 possibility of pulling organisms has been raised as a

25 means to accrue more patients. Pulling a cross

studies within an indication or pulling across

indications. If it's sound to pull organisms

retrospectively, we may obtain a better powered

assessment of moxifloxacin efficacy in resistant

pneumococcal infection.

First, I would like to look at what we can

learn from the pneumonia studies as a whole. 0140 is

our largest source of pneumococcal isolates that are

resistant or of intermediate pen. susceptibility.

Another controlled study, D96026, and an uncontrolled

study, D96025, also provide a handful of resistant or

intermediately susceptible isolates.

If we sum these up, you can see that a

slightly higher efficacy rate is observed for the

moxifloxacin treated patients who had frankly

resistant isolates. An efficacy rate that approaches

that which was seen for pneumococcal infections over

all for this drug is achieved with the patients from

whomintermediatelysusceptible isolates are cultured.

I've raised the question of pulling data

and i would like to take a minute to make explicit

some of the questions inherent in this. Can we go

back and retrospectively combine data from a number of

studies that were not designed to have their data

combined across studies of different design within the

1   same indication.

2   From the previous slide you can see that

3   some of these studies were controlled and some

4   uncontrolled. Some blinded, some open label.

5   Different studies had patients evaluated for test of

6   cure at different points in time following completion

7   of therapy.

8   Is it reasonable to pull data across

9   indications? When we looked at this NDA and looked at

10 the different indications included in it, the one

11 other site of infection that we thought may be

12 amenable to this kind of analysis was sinusitis. The

13 reasons for that are that the sinuses are another

14 point along the respiratory tract and they are

15 normally sterile space that is closed.

16   So I'm going to take a minute and talk

17 about the sinusitis indication. This slide is mostly

18 a discussion of efficacy in sinusitis overall. I've

19 p cked a representative study, 100107, which compared

20 moxifloxacin to cefuroxime in a lo-day regimen.

21   The per protocol and intent to treat

22 analyses both demonstrated equivalence between the two

23 treatment arms by the statistical criteria that were

24 perspectively determined for this study.

25   I would like to point out that the medical

1 officer analysis for this study differs slightly from

2 that of the sponsor in that the medical officer

3 determined the test of cure visit that took place a

4 little bit later at 27 to 31 days following completion

5 of therapy. Again, for those of you who may have seen

6 other numbers on this, this is the medical officer

7 analysis and it's a later follow-up visit.

8 How can we use the sinusitis indication to

9 learn something about efficacy of moxifloxacin in

10 pneumococcal infections? Probably the best study for

11 looking at this is No. D96023 which used the only

12 method that FDA is currently considering appropriate

13 for obtaining sinus specimens for microbiologic

14 efficacy analysis and that is antral tap studies.

15 A number of pneumococcal isolates were

16 cultured in D96023 which was an uncontrolled study.

17 All of the patients in this study were treated with

18 moxifloxacin. Thirty of them had a susceptible

19 isolate, six a resistant isolate, and nine an isolate

20 of intermediate penicillin susceptibility.

21 I think you can see from looking at the

22 cure rates on the bottom row that they were high and

23 consistent between the three groups. This is

24 providing us a slightly different look atmoxifloxacin

25 efficacy in pneumococcal and resistant pneumococcal

1   infections.

2   I think we can say that clinical

3   equivalence of moxifloxacin to approve comparators has

4   been demonstrated in all four indications including

5   sinusitis and community acquired pneumonia, data step

6   pneumoniae.   However, the efficacy rate for

7   moxifloxacin was less than that of high dose

8   amoxicillin for the treatment of pneumonia in two

9   subpopulations of interest.   Those are patients who

10   had frankly penicillin resistant strains of

11   pneumococcus and those patients who had pneumococcal

12   bacteremia of any degree of susceptibility or

13   resistance to penicillin.

14   As you've heard, preclinical data, PKPD

15   ratios, and efficacy against penicillin intermediate

16   strains of pneumococcus are supportive of this

17   clinical efficacy.   I think the question remains

18   whether or not there are sufficient data to support a

19   claim of efficacy in the treatment of pneumonia and/or

20   sinusitis due to penicillin resistant pneumococcus.

21   Are there any questions?

22   DR. RELLER: Dr. Murray.

23   DR. MURRAY: Yes, just one. The severity

24   of pneumonia, do you have a sense of that? We heard

25   data yesterday about how many of the pneumonias were

1 classified as severe.

2 DR. MEYERHOFF: I cannot give you that

3 kind of breakdown. All of these patients were

4 amenable to oral therapy. At the same time we can see

5 that some proportion of them were bacteremic. I can't

6 give you a sense beyond that.

7 DR. RELLER: Gordon.

8 DR. ARCHER: You didn't mention it but I

9 assume that the isolates that were penicillin

10 resistant were all moxifloxacin susceptible at the

11 same MICs that we heard this morning? And do you have

12 any of the relapse isolates from those two patients?

13 Were they more resistant to moxifloxacin?

14 DR. MEYERHOFF: In answer to your first

15 question, I believe yes, that's true. No, I don't

16 have MIC data on those repeat isolates.

17 DR. ARCHER: Does the sponsor have such

18 data?

19 DR. CHURCH   Dr. Meyerhoff is accurate

20 when she is stating about the MICs to moxifloxacin in

21 those patients. They were all susceptible. With

22 regards to MICs done afterwards, I believe there are

23 not and I'll have to look at any of my colleagues.

24 Barbara Painter? That's correct. There are no MICs

25 after the initial ones.

1   DR. RELLER: So the organism was recovered

2   after therapy but no testing was done for the agent to

3   which the patient -- with which the patient failed?

4   DR. CHURCH: Probably because the patients

5   -- are you talking about the initial patients that Dr.

6   Meyerhoff showed that are failures or patients that

7   were cured?

8   DR. RELLER: No, the failures.

9   DR. CHURCH: The failures. I do not have

10 that information it sounds like.

11 DR. MEYERHOFF: They didn't say they were

12 microbiologic failures. We're not sure of that

13 actually.

14 DR. RELLER: I understand that. That's

15 why I'm asking the question. I mean, actually Dr.

16 Meyerhoff specifically said in her addressing

17 efficacy, her numbers were based on clinical efficacy.

18 Is that correct?

19 DR. MEYERHOFF: That's correct.

20 DR. RELLER: I mean, we don't know. If

21 mean, if they were not microbiological failures, then,

22 of course, we wouldn't have any post therapy MICs.

23 DR. MEYERHOFF: There were no cultures in

24 the follow-ups.

25 DR. RELLER: Meaning they were not done in

1 the clinical failures or they were done and no

2 organism was recovered?

3   DR. MEYERHOFF: Not done.

4   DR. RELLER: Thank you.

5   DR. MEYERHOFF: You're welcome.

6   DR. RELLER: Dr. Christie.

7   DR. CHRISTIE: To look at the severity of

8 this in another way because I think it's important.

9 You did say that 80 percent of the patients were

10 hospitalized in 0140? I guess I wonder in that

11 population could you break out how many received moxi

12 versus hydomcymox. Could you break out as well to the

13 resistance in the bacteremic cases.

14   DR. MURRAY: These weren't U.S. based

15 studies thought, Were they?

16   DR. MEYERHOFF: No, they weren't. They

17 were done in probably 30 or 40 foreign countries.

18   DR. MURRAY: So hospitalization should not

19 be taken as a sign of severity necessarily?

20   DR. MEYERHOFF: The sponsor is saying

21 that's correct. I think that's a caveat we have to

22 bear in mind when we look at these patients. They are

23 sort of mixed. If you would compare them to an

24 pneumonia patient we would see in this country, they

25 could get oral therapy but 80 percent of them needed

1   to be in the hospital by somebody's judgment.

2   DR. RELLER: Dr. Platt.

3   DR. PLATT: This is a question actually

4   for Dr. Church left over from this morning but I think

5   it fits here better than anywhere else. Although the

6   common treatment course is 10 days, you showed a

7   serial passage for resistance lasting either six or

8   eight days for what looked like a single strain of

9   staph. aureus and strep. pneumoniae. Do you have more

10   data that takes a larger number of organisms out well

11   beyond the usual treatment course?

12   DR. CHURCH: No, we do not.

13   DR. RELLER: I'd like to thank Dr.

14   Meyerhoff for bringing us to this point before lunch.

15   Despite the written agenda, we will -- well, in accord

16   with the written agenda despite the time that we

17   stopped, we will reconvene promptly at 1:00, please.

18   (Whereupon, at 12:02 p.m. off the record

19   until 1:01 p.m.)

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1   A-F-T-E-R-N-O-O-N   S-E-S-S-I-O-N

2   1:01 p.m.

3   ACTING CHAIRMAN RELLER: We're ready to

4   begin the afternoon session. First will be the FDA

5   presentation about safety by Dr. Leonard Sacks.

6   Dr. Sacks.

7   DR. SACKS: Good afternoon. I'm Leonard

8   Sacks, I'm the Medical Officer at the Division of

9   Special Pathogens, and what I'll be doing over

10   approximately the next 20 minutes is reviewing the

11   FDA's perspective on the safety of moxifloxacin as

12   demonstrated to us in NDA 21085.

13   My safety review will be divided into two

14   broad sections. Firstly, I'll be covering issues of

15   general safety, and then I will move on specifically

16   to issues of cardiac safety, and in the discussion of

17   cardiac safety I will move across the various topics

18   that have been addressed this morning, the in vitro

19   information that we have, the animal studies, the

20   Phase I and II study data, and finally the big

21   clinical database of Phase III trials.

22   In terms of general safety, this is the

23   database that we are looking at. We are looking at

24   4,370 patients treated with the recommended 400

25   milligram oral dose of moxifloxacin. There were 557

1   patients treated with 200 milligrams a day, and we are

2   looking at 3,415 patients on comparator agents.

3   This slide demonstrates the most common

4   adverse events occurring in at least three percent of

5   patients treated with moxifloxacin or comparator

6   agents. These are drug-related adverse events. As you

7   can see, the rates here are slightly different from

8   those reported this morning, which referred to all

9   adverse events, and they are pretty comparable between

10 moxifloxacin and comparator. All events, 32 percent

11 in moxifloxacin treated patients, 30 percent in

12 comparator treated patients, far and away the

13 commonest adverse events reported were nausea and

14 diarrhea, gastrointestinal occurring in respect to the

15 agent, seven percent of the moxifloxacin treated

16 patients, six and five percent of the comparator

17 treated patients. Headache was found in three percent

18 of both. Dizziness was slightly more common in the

19 moxifloxacin treated patients, three percent as

20 opposed to two percent.

21   What I then did **was** summarize some of the

22 known quinolone-related toxicities, just to see the

23 effects of **moxif** loxacin in this regard, and the

24 information here is similar to that that was presented

25 earlier this morning. Phototoxicity, as far as I

1 could establish, was reported in four patients on the

2 moxifloxacin arm, two of these were actually

3 attributed to the drug, two were not. Hemolytic

4 uremic syndrome was not described in the database at

5 all. Tendon rupture was not reported in the database

6 either, although there were two patients with Achilles

7 tendon pain, and there were no cases in the comparator

8 group.

9 Looking at the question of hypoglycemia,

10 this was seen in five percent of the moxifloxacin

11 treated patients, four percent of comparator treated

12 patients.

13 Looking for the specific effects on the

14 central nervous system, we noted previously that

15 dizziness was slightly more frequent in the

16 moxifloxacin treated patients. In this example of all

17 adverse events, we see a rate of four percent among

18 moxifloxacin treated patients, two percent among

19 comparator treated patients. Convulsions were

20 described in two patients on moxifloxacin and two

21 patients on the comparator, no significant difference,

22 and abnormal liver functions as a whole were reported

23 in two percent of both moxifloxacin treated patients

24 and comparator treated patients.

25 Given the current concern about quinolone

1   toxicity, hepatotoxicity, I'm just going to go into

2   the issue of liver functions in a little bit more

3   detail.   This slide shows the treatment emergent

4   abnormalities in AST, ALT, alkaline phosphatase and

5   total bilirubin.   These abnormalities, I must point

6   out, were categorically defined as either normal or

7   abnormal depending on the cutoffs for each of the

8   studies, and we see that the rates are very similar

9   across the board. They are seven percent for elevated

10   AST on the moxifloxacin, and eight percent among

11   controls.   ALT was equivalent among the two arms.

12   Alkaline phosphatase four and three, and bilirubin

13   three percent of the moxifloxacin treated patients

14   were elevated, two percent of the comparator treated

15   patients.

16   This was an attempt to climb the NDA

17   iceberg and take a look from the very top at the most

18   toxic possible liver events to try and capture any

19   cases of drug-induced hepatitis. And, what I've done

20   here is presented patients who had at least a two-fold

21   increase in AST and ALT and bilirubin related to

22   therapy, and these patients were to have at least one

23   of these parameters significantly abnormal.   Using

24   this analysis, you can see that there were seven

25   patients identified on the database, four in the

1 moxifloxacin treated group, three in the Cephalexin,

2 three on comparator agents as listed there, and I've

3 listed the individual results pre and post treatment -

4 - yes, pre and post treatment, the results for each of

5 the parameters, and here are the outcomes where they

6 were available. These were resolved, this **was**

7 reported as improved. This patient who developed an

8 on treatment bilirubin of 7.2 **was** reported to have a

9 bilirubin of 2.2 milligrams per deciliter five days

10 after stopping treatment, and we know that the patient

11 was listed as a clinical cure after 30 days, although

12 the final outcome of the adverse event I'm sorry, I

13 don't have the information on. These are the three

14 comparative patients, just to show comparative levels

15 of treatment emergent abnormalities.

16 Let's move on now to examine the deaths in

17 the study. This presentation, I must mention, is

18 different from that that was shared with us this

19 morning. These are absolute numbers, these are not

20 normalized for numbers of patients. This just

21 illustrates the 38 deaths on the patient database

22 according to when they occurred, and these are the

23 deaths that occurred while on treatment, three on

24 moxifloxacin, one on comparator. Remember again that

25 these are not normalized for the patient denominators.

1 These are the deaths that occurred over a period of

2 time, and these are deaths which occurred after 30

3 days following treatment.

4   I think one of the purposes of this slide

5 is to illustrate that there are differences in the

6 death rate according to when these are analyzed.

7 Overall death rates, these were calculated for all

8 patients on the database. This includes both patients

9 on the 200 milligram and the 400 milligram dose and

10 patients over the entire period of the study. This

11 incorporates the latter data points, and you can see

12 that these death rates are very similar for

13 moxifloxacin and comparator treated patients, .45

14 percent and .47 percent, respectively.

15   I'm now going to change gears and move on

16 to the cardiac safety, just to cover a couple of

17 issues. Let's move on to the next slide which

18 addresses some of the data that you've already seen on

19 the in vitro models, just to point out that the effect

20 on the delayed inward rectifier current, the Ikr, we

21 see that in one of three experiments on models

22 moxifloxacin was able to block this particular ionic

23 channel in mouse atrial cells at a concentration of 75

24 micromolar as compared to, that's probably .75

25 micromolar, as compared with .23 micromolar in

1   sparfloxacin, so it's about one third as potent as

2   sparfloxacin.

3   For completeness, I believe that the

4   status of the IKs is less well established in terms of

5   its effect on the QT interval, but moxifloxacin did

6   show some blockage if the IKs, and, perhaps, more

7   importantly the action potential duration was

8   prolonged by moxifloxacin as a concentration of 50

9   micromolar and sparfloxacin at a much lower

10   concentration, three micromolar.

11   Let's turn to the animal studies. This is

12   a busy slide summarizing a number of animal studies.

13   Most have been performed, as you will see, in beagle

14   dogs, looking at various doses, various infusion rates

15   in combinations with other medications. The point I

16   want to highlight on this slide is basically the

17   reasons for getting the most striking QT

18   prolongations, and you will note that this is related

19   predominantly to the rate of infusion and, obviously,

20   to the dose of the drug, and here you can see a 69

21   millisecond prolongation in dogs who were given 30

22   milligrams per kilogram as a bolus. Here you can see

23   that high infusion rates produce the same sort of

24   effect, and a 30 milligram per kilogram dose every 15

25   minutes gave a 64 millisecond prolongation. Giving

1   Sotalol concurrently does not seem like a good idea.

2   There's 113. And, when you give extreme overdoses,

3   such as was demonstrated in this study, you can

4   obviously get very prolonged QT intervals and clinical

5   episodes of ventricular -- the Torsade de Pointes and

6   ventricular extrasystoles.

            Let's move on to the next slide. We are

8   now turning to a little bit of human data. This may

9   be slightly different from the slides you've seen

10   earlier presented by the sponsor.   In this case, we

11   are looking at the change in QTc interval related to

12   treatment, and this is a population of patients who

13   were given single doses of oral treatment, anything

14   over and above 200 milligrams, 181 patients in the

15   group. Again, the points here are that we have a

16   regression line there which shows a positive slope,

17   it's a shallow slope, but it is, as you see -- it's

18   not showing anymore, I apologize -- it's significantly

19   different from zero with a p value of .001.   The

20   superimposed   mauve   lines   there   indicate   the

21   anticipated serum concentrations after a single oral

22   dose of 400 milligrams taken from a subpopulation and

23   analyzed by members of our staff.   The dotted line

24   shows the mean and the standard deviation on either

25   side, so that's where the bulk of these concentrations

1 seem to fit after the first dose of 400 milligrams.

2 Let's move on to the next slide. Just in

3 terms of the Phase I and Phase II clinical

4 participants, these were mean prolongations of the QTc

5 that were found in that population group. You can see

6 there are 112 patients treated with a recommended 400

7 milligram oral dose, a mean prolongation of 6.9

8 milliseconds with quite a wide range. Those treated

9 with intravenous infusions of 400 milligrams at

10 varying periods of time developed more marked QTc

11 prolongations, mean prolongations, 28 subjects, the

12 mean prolongation of 12.1, and a mean prolongation was

13 increased, at least the mean prolongation was detected

14 in patients on placebo, 3.5, which does emphasize that

15 there is some variability in placebo treated patients.

16 Let's move on to the next slide. I'm not

17 going to cover this in any detail, I think we've been

18 through the definitions of outliers before. Just to

19 bear in mind that we were a little bit more lenient on

20 females, because they start off with a longer QT

21 interval to normally.

22 Next slide, so in terms of the three

23 categories, normal, borderline and prolonged, what we

24 are looking at in this shift analysis is patients on

25 a 400 milligram oral dose who changed from their

1 baseline status, and of the 107 patients who had a

2 normal baseline QT interval you can see that nine

3 percent of them developedborderline prolongations and

4 2.8 percent of them developed prolonged QT

5 prolongations, as compared with 2.4 and 2.4 in the

6 comparator. Note again, small numbers of patients,

7 we've got a total of 41 in that group. There were no

8 patients of the 12 patients with borderline at

9 baseline who developed marked prolongations, whereas

10 here one of the five patients with borderline

11 developed marked or significant prolongation on

12 treatment.

13 Let's move on to the next slide. This is

14 really just a summary of the Phase I and Phase II

15 clinical data, trying to establish whether there were

16 any events which looked like actual arrhythmias as a

17 result of the drug. The first one was described as an

18 elderly woman, who was given a single 200 milligram

19 oral dose of moxifloxacin, she developed a subjective

20 complaint of irregular heartbeat 12 hours after the

21 dose, and an ECG which was performed after the event

22 was normal. And, the relationship with this is

23 remote. The other patient was a young healthy male.

24 This male apparently tolerated a 33-minute infusion of

25 400 milligrams of moxifloxacin. He remained on the IV

1 and 11 minutes later he developed weakness, he

2 developed nausea and a sinus bradycardia of 35 to 40

3 per minute. He fainted and there was an episode of

4 asystole described for several seconds. Cardiac

5 resuscitation was implemented, he developed a

6 ventricular rhythm, junctional and sinus rhythm with

7 no sequelae. The events were analyzed by two

8 cardiologists, and they were deemed a vasovagal

9 syncope.

10 Let's move on to the next slide. At this

11 point I think it became -- or, in fact, earlier on in

12 the Phase I and Phase II studies, it was apparent that

13 further investigations should be implemented to look

14 at the broader clinical database in terms of the

15 effects on the QT interval. The protocols, all

16 ongoing protocols were modified as of May, '97 to

17 incorporate a baseline and a follow-up ECG two to six

18 hours after the dose. Also, there were exclusions

19 included in this modification, in this addendum.

20 Patients with baseline prolongations of the ECG were

21 excluded from QT analysis, and also patients on

22 medications known to prolong the QT interval were

23 prohibited, and this included many that we discussed

24 this morning of the antiarrhythmic group primarily,

25 except for terfenadine, so amiodarone, sotalol,

1 disopyramide, quinidine, procainamide and terfenadine

2 were not permitted.

3 Let's move on to the next slide. This is

4 the size of the database. We are looking at 8,341

5 patients valid for safety. This was before the four

6 month safety update, and that will account for some

7 small differences between the company's figures and

8 some of our's. Two thousand, one hundred and thirteen

9 of the patients had ECGs. You'll notice that in large

10 number, 1,002 patients, were excluded for technical

11 reasons, and I will go into some of these in a little

12 bit more detail, and we are left with 1,111 patients

13 who had paired valid ECGs of reasonable quality, 559

14 of these were on 400 milligrams, the recommended dose

15 of moxifloxacin, 37 on the low dose of 200 milligrams,

16 and 515 patients on the comparator.

17 So, let's look at some of the reasons for

18 excluding patients, next slide please, and you can see

19 that a lot of these are practical reasons. In a large

20 percentage of patients, the ECGs were not paired, the

21 relative timing of the ECGs was not known, which was

22 first, which was subsequent. They did not fall into

23 the six-hour time window. The quality was not

24 interpretable, scale may have been missing. There was

25 a restriction on the number of PVCs that allowed

1 interpretation of the QT interval, both in the pre and

2 the post dosing ECG, and atrial fibrillation also made

3 the calculation of the QT interval unreliable.

4 Let's move on to the next slide. This is

5 similar to the slide that I showed you on the mean QTc

6 prolongation of Phase I and II studies. This is in

7 the general clinical database, and we see that of the

8 patients with valid paired ECGs, patients on the

9 recommended 400 milligram dose, 611 patients in this

10 particular calculation. The mean prolongation here was

11 five milliseconds. I've mentioned that the company

12 presented this information based on the four month

13 safety update and they got a figure of six

14 milliseconds. Here is the 95 percent confidence

15 interval around that mean. In parentheses I've just

16 included the uncorrected QT intervals.

17 Just to compare this with the 136 patients

18 in the comparator group who were treated with

19 clarithromycin, and you see that the mean prolongation

20 here was two, with a confidence interval of minus 2 to

21 6, and overall this is all comparators, including the

22 clarithromycin treated patients, there was really no

23 change in the -- no mean change in the QTc interval on

24 treatment.

25 Next slide. This is another attempt to

look at outliers, in terms of the bigger clinical population, and what we see here is of the 424 patients who started off with normal QT intervals pre-treatment, there were 15 percent who developed borderline prolongations and 2.4 percent who developed significant prolongations after dosing. Compare this with ten percent and 2.6 percent in the comparator, and a similar sort of effect noticed for borderline. Those who started off, 100 patients starting off with borderline prolongations, 26 percent developed prolongations, and on a comparator there were 90 patients starting off with borderline prolongations, 21 percent developed prolongations on treatment.

Let's move on to the next slide. This is, again, another look at the tip of the iceberg. This was an attempt to characterize the most severe aberrations of QT abnormalities, and this was just looking at patients who developed a QT interval of greater than 500 milliseconds at any interval during the study. This could have been pre or post. And, what you see here is that there were three patients who developed QTc prolongations on moxifloxacin of greater than 500 milliseconds. There were three patients in the comparator group who started off with 500 milliseconds or greater prolongations, and

1 normalized on comparator treatment, there was one

2 patient on a comparator arm who increased from 494 to

3 over 500.

4 It has been pointed out to me, and,

5 perhaps, the company will address this later on, that

6 one of these patients was shown to have been misread

7 and the speed of the ECG tracing was misinterpreted,

8 but they will have to provide that information.

9 So, based on our information, we had three

10 out of 559 patients treated with moxifloxacin who

11 developed treatment emergent QTcs of greater than 500

12 milliseconds, compared with one out of 515 among the

13 comparator, again, very small numbers to make any

14 statistical inferences.

15 Can we move on to the next slide? This

16 was another attempt to look at predisposing conditions

17 resulting in prolongations of the QTc, and I selected

18 the one which certainly impressed me the most. This

19 is looking at the effects of hypokalemia, and you can

20 see that this is looking at prolongations, treatment

21 emergent prolongations of the QTc of between 30 to 60

22 milliseconds and greater than 60. These intermediate

23 prolongations among patients with normal potassiums

24 before treatment, there were 12 percent of the

25 moxifloxacin treated patients who developed

1 prolongations of intermediate severity. Once you

2 looked at the populations who were hypokalemic, this

3 figure went up to 18.9 percent. Notice that in the

4 comparator there **was** no increase. When we look at

5 those who developed more extreme prolongations of

6 greater than 60 milliseconds, 1.7 percent of the

7 patients who were normokalemic on moxifloxacin had

8 extreme prolongations before with normal potassiums

9 and when you looked at the population with low

10 potassiums that went up to 8.1 percent, which was

11 statistically significantly different. Note again

12 that the comparator didn't show the same increase.

13   Can we move on to the next slide? This is

14 another attempt to try and look at clinical events

15 which may be telling us that either there were

16 arrhythmias or surrogates for arrhythmia, and across

17 the board you can see that these event rates are very

18 similar between the 3,000 odd patients reported for

19 the 400 milligram moxifloxacin dose and the control

20 dose.

21   I do want to draw your attention to atrial

22 fibrillation which was significantly more common,

23 there were 12 cases in the moxifloxacin treated data

24 group, as compared to two in the control group.

25   Okay, I think we can move on to the next

1   slide, so I'm going to summarize by saying that we

2   noted that moxifloxacin blocked the Ikr at a

3   concentration approximately three times that of

4   sparfloxacin. It prolonged the action potential

5   duration by about -- at concentrations of 50

6   micromolar compared to three micromolar for

7   sparfloxacin. It showed a dose-related prolongation,

8   both in animals and in humans. The mean prolongation

9   was five milliseconds in this database, it appears to

10   be six when you look at the revised database, on the

11   oral dose, 12 milliseconds on the intravenous.

12   Outlier analysis showed three or possibly two out of

13   the 559 treated moxifloxacin patients with QTc

14   emergent values of greater than 500, but otherwise the

15   outliers looked pretty similar between the two groups.

16   I wanted to draw your attention again to

17   the effects of hypokalemia on moxifloxacin-induced QT

18   changes.

19   Now, I think we've revised the order of

20   the program, so I will hold until we have the next

21   presentation, before going on to the questions.

22   Okay, so without further ado, let me

23   introduce Allen Brinker, who will present some

24   information on the post-marketing experience with QTc

25   prolongations.

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1   DR. BRINKER: We're ready for the first

2   slide. Very good, thanks for the introduction,

3   Leonard. My name is Allen Brinker, and I'm going to

4   be presenting some data to you this afternoon from the

5   post-marketing environment, specifically reporting

6   rates for serious cardiac dysrhythmias among the

7   marketed   fluoroquinolones;   azythromycin,

8   clarithromycin and cefuroxime.

9   My presentation will be divided into the

10   following categories, an introduction to reporting

11   rates, the strength and limitations of spontaneous

12   adverse event reports, the methods that I utilized to

13   calculate these reporting rates, a very important

14   topic that I will come back to again and again is

15   interpretation of these reporting rates, given some

16   comments about the tyranny of small numbers and other

17   such comments about making a lot out of very small

18   numbers, and finally results of discussion.

19   Next slide, please. In general, a crude

20   reporting rate can be calculated as the number of

21   spontaneous domestic reported cases over some estimate

22   of domestic use.   In this **case,** it's domestic

23   prescriptions, and this can be calculated for any

24   specific interval of marketing or year on the market.

25   I'm going to be using a two-year interval this

1   afternoon, because some of these drugs, specifically,

2   sparfloxacin, has only been on the market for two

3   years.

4   Next slide, please. The numerator comes

5   to us from our spontaneous case reports database or

6   AERS database, which include the spontaneous reactions

7   collected by the FDA's -- and I just mentioned the

8   acronym, Adverse Event Reporting System, or AERS.

9   Next slide, please. The denominator is

10   total prescriptions, which comes to us from the IMS

11   HEALTH National Prescription Audit, or NPA. The NPA

12   is a proprietary product that we use internally within

13   the FDA, and the numbers that I'm going to be

14   presenting to you this afternoon are used with

15   permission from IMS HEALTH.

16   Next slide, please. Just a little bit of

17   background on the spontaneous adverse events

18   collection process. In our country we utilize a

19   passive surveillance system to collect spontaneous

20   reports from clinicians, nurses, pharmacists and

21   individuals. This is sometimes referred to by the

22   division that collects these reports, the MedWatch

23   Division. This is a cost-effective process for the

24   evaluation of safety in the post-marketing

25   environment, and it is most applicable for qualitative

1 signal generation. Currently, we receive

2 approximately 250,000 such adverse case reports per

3 year.

4 Next slide, please. There are some

5 substantial limitations with regard to a spontaneous

6 adverse reporting system, the biggest of which is

7 probably reporting, or as we refer to it, under-

8 reporting, in that we receive next to none or maybe 15

9 percent of incident cases within the population, and

10 these statistics for how many cases are actually

11 reported to us vary for the specific adverse event.

12 There are studies that suggest that we receive a

13 higher proportion of such reports for serious adverse

14 events, such as liver failure, and probably

15 practically none for trivial or clinically mild

16 processes. We know that spontaneous reports are

17 influenced by publicity, and there are more reports

18 early in a market life of a drug, and this has been

19 termed the Weber phenomenon.

20 Next slide, please. As far as case

21 ascertainment used in this analysis, because of the

22 difficulty in collection, in classification and

23 detection of Torsade de Pointes, I utilized the coding

24 term ventricular arrhythmias in cardiac arrest to

25 collect cases for this reporting rate. I included all

1 unduplicated domestic cases, and as I said earlier

2 this **was** calculated, or these calculations were

3 performed after the second market year.

4 Next slide, please. I will be presenting

5 rates to you this afternoon that have been adjusted --

6 I'll be presenting both, actually, but I will be

7 specifically highlighting those that have been

8 adjusted for secular trend. Secular trend is based on

9 the observation that the reporting of adverse events

10 has increased since the early 1980s. Next slide,

11 please. That phenomenon is highlighted on this

12 particular slide.

13 Next slide, please. Adjustment for

14 secular trend increases the weight of cases that were

15 reported in the past. It's applicable in a comparison

16 of drugs, drug products first marketed in different

17 years, and I will highlight in this analysis we had

18 drugs spanning ten years, and so it was very important

19 to consider secular trend, and I will be presenting

20 both crude and adjusted rates.

21 Next slide, please. General limitations

22 that I want to touch base with again include that

23 reporting rates do not equal incidence rates. The

24 relationship between reporting rates and incidence is

25 unknown, and comparisons of reporting rates do not

1 include the unique benefits of each agent. This is

2 sometimes referred to as a risk benefit ratio or risk

3 benefit analysis.

4   Next slide, please. Further limitations

5 include the biases for comparisons between drug

6 products, given differences in indications and off-

7 label use, the patient population where the drugs are

8 used, the prescriber specialty, and the particular

9 drug sponsor.

10   Next slide, please. I also want to

11 highlight whether or not these data are most

12 applicable for a qualitative or quantitative

13 evaluation, and I will be presenting both. For the

14 subjective interpretation of the data, one must have

15 a signal threshold, which you might refer to as a rate

16 ratio, and conjecture and literature reports cite a

17 rate ratio, a relative risk of two or three below

18 which epidemiologic or observational data probably

19 can't distinguish noise from association, and that

20 would probably be an underestimate for these data.

21   Another way to do that would be objective,

22 and that would be application of 95 percent confidence

23 intervals. However, because the distribution of these

24 data are uncertain I do this with trepidation.

25 Fortunately, in my conclusions that I draw from these

1   analyses you come out with the same impression.

2   Next slide, please. Given all that, let's

3   press on with the results. This table lists domestic

4   case reports in the first two years that were returned

5   under the term ventricular arrhythmias and cardiac

6   arrest and usage data for the first two years of

7   marketing for the agents specified in my introduction.

8   These agents are listed by year of introduction over

9   here. The prescriptions over here, I want to note,

10   are given to you in terms of thousands, so for the

11   first agent here, norfloxacin, that's 2.7 million

12   prescriptions. As we go down the list I want to make

13   one important point, and that is that for both

14   cefuroxime and for sparfloxacin they both had only one

15   case, and given the qualitative nature of these data

16   that raises substantially our uncertainty with regard

17   to any point estimate calculated for these particular

18   agents, and that's magnified even further when we

19   consider that sparfloxacin introduced in 1997 only had

20   49,000 prescriptions in its first two years of use,

21   first two years on the market. So, in comparison to

22   3.8 million for cefuroxime, so as you will see, I will

23   come back to sparfloxacin. The jury is out with

24   regard to this agent.

25   Next slide, please. So, this slide

1   presents the crude and adjusted two year reporting

2   rates for these specific individuals, or these

3   specific agents, and they are ranked on adjusted

4   reporting rate right over here. The first thing I

5   want to point out is the reporting rates that I have

6   listed here are per 10 million prescriptions. So, for

7   cefuroxime the first -- that one case represents an

8   adjusted reporting rate of three per 10 million

9   prescriptions, so in absolute magnitude these are very

10   infrequent events, or at least these are reported very

11   infrequently.

12   The second thing I want to point out to

13   you from this list is that sparfloxacin comes in with

14   an adjusted reporting rate of 145, which sticks out

15   like a sore thumb in comparison to the others. I

16   can't -- I don't know what to make of that number,

17   other than it's based on so much uncertainty given the

18   limited use and the one case that it really can't be

19   isolated.

20   Now then, with regard to interpretation of

21   this data, I said that I will be performing, or I

22   would subject them to both a qualitative and

23   quantitative analysis. One way to look at these data

24   would be to normalize to the lowest individual here,

25   the one with the lowest rate, cefuroxime, in which

1 case your first agent, cipro, comes in with a rate

2 ratio of nine, and then all the rest of these agents,

3 includingreallyclarithromycinbecausethe difference

4 between nine and 30 is only three-fold, would really

5 follow -- there would be a gap between examination of

6 this agent and the rest of the agents, which aren't

7 even necessarily a comparison -- which include a

8 comparison between classes, given that this is

9 cephalosporin and the issue we are talking about today

10 is for a fluoroquinolone. So, I don't necessarily

11 think that would be the most valid comparison to

12 normalize to cefuroxime. It is one way to look at the

13 data. I would probably prefer to normalize to

14 ciprofloxacin and group all of these agents probably

15 in the same - qualitatively as having basically the

16 same reporting rate with a difference of three-fold

17 between them.

18 Next slide. I highlight those points

19 right here. Qualitative assessment is going to vary

20 with your threshold that you choose. It's also going

21 to vary with your reference agent, whether or not you

22 choose a drug with similar agents, and choose

23 cefuroxime, or whether you normalize to ciprofloxacin

24 and do it by class.

25 Next slide, please. However, I find no

1   qualitative difference seen in the reporting of this

2   adverse event among these antibiotics with the

3   possible exception of sparfloxacin.

4   Next slide, please.   In this

5   interpretation of the data I've given you 95 percent

6   confidence intervals for the adjusted reporting rates,

7   and I want to point out that the confidence bands

8   overlap basicallywiththe exception of clarithromycin

9   seems to stand out a little bit in comparison to

10   cefuroxime, but given the nature of these data I would

11   not call attention to this difference. I also want to

12   call attention to sparfloxacin, yet again you really

13   see the effect of one case and a low denominator with

14   a confidence interval of 3.7 to 807, that's so far out

15   there as to make it uninterpretable.

16   Next slide, please. So, these data

17   suggest no or very limited quantitative differences

18   seen in the reporting of this adverse event among

19   these antibiotics. I note the possible exception of

20   sparfloxacin.

21   Next slide, please.   With regard to

22   sparfloxacin, given its limited use in the one case

23   these data cannot be used to isolate it.   It is

24   interesting to note that among these antibiotics it

25   stands out and it's the one whose label actually

1 includes the incidence of QT prolongation in

2 comparison to erythromycin and cefaclor in the label.

3 Next slide, please. As far as a

4 supplemental sensitivity analysis, I was unable to

5 differentiate between these agents in this analysis,

6 and so I went back and using the same coding term I

7 performed this exercise in a comparison of cisapride

8 versus omeprazol, and this product was chosen because

9 it actually leads the list of adverse drug reports for

10 QT prolongation and Torsade.

11 Next slide, please. And, this table

12 summarizes those findings. Okay. There are four cases

13 for omeprazol in the first two years versus 27 for

14 cisapride, gives you an adjusted reporting rate of 13

15 versus 63, which is almost a five-fold difference, and

16 it's interesting to note that the 95 percent

17 confidence intervals are divergent for these two point

18 estimates.

19 So, next slide, please, I believe that

20 this actually suggests that we can use these agents to

21 possibly detect a difference with regard to certain

22 agents in a comparison of agents with similar use.

23 Next slide, please. So, I want to

24 finalize with what I believe is the take home message,

25 and that is that I chose to examine a rather general

1 term of cardiac arrhythmias and it doesn't really

2 address the issue of QT prolongation with specific --

3 specifically for moxifloxacin.

4   Leonard, if you'll join me now we'll see

5 if there are any questions.

6   ACTING CHAIRMAN RELLER: Questions for

7 Dr.s Sacks and Brinker.

8   Yes, Dr. Ruskin.

9   DR. RUSKIN: I have a question for Dr.

10 Sacks. You showed a mortality slide that confused me,

11 and I'm probably just being dense about this, but I

12 was impressed with the data that Bayer showed, and you

13 described what you said were raw mortality rates, yet

14 at the bottom you showed percentages. I don't know

15 how you get a percentage without using a denominator,

16 yet you said you hadn't used a denominator. So, can

17 you unconfuse me?

18   DR. SACKS: Sure, or I'll try. The

19 graphic just represented the numbers of patients

20 dying, but the calculated value was based on the

21 denominator of all patients in the safety database.

22   Now, the fact that you may be confused

23 between the company's data and mine is based on the

24 fact that I've included six deaths on 200 milligram

25 doses which were not included by the company, and

1 they've included the denominator for those patients on

2 the 200 milligrams, or at least they've excluded the

3 denominator for those 200 milligram patients, whereas

4 we've included them. The other difference between our

5 data analyses was that they excluded the patients who

6 died after 30 days, where you would have seen that

7 there were a couple of disparities in the number of

8 deaths after day 30. And, in fact, we went through

9 this at some length.

10   There are many different ways in which you

11 can look at that data, in terms of indications, in

12 terms of dosages, in terms of duration of follow up,

13 that give substantially different results.

14   DR. RUSKIN: Is it fair to say then that

15 if you include all patients exposed to moxifloxacin at

16 any dose and compare those with the comparators that

17 there was no difference in mortality?

18   MR. SACKS: Across all time frames, that

19 was our impression, yes.

20   DR. RUSKIN: What about leaving out the

21 late deaths? If you leave out the greater than --

22   MR. SACKS: Perhaps, we could get back to

23 the slide.   I haven't done the calculation

24 specifically for that interval. I'm not sure if

25 anyone in the audience can help me with that. I think

1   we do have some calculations. The one with the bar

2   graph, perhaps, it will just give you --

3   DR. KWEDER: Slide eight, John.

4   DR. SACKS: Yes. I think what you see are

5   the number of deaths after 30 days, there were one,

6   two, three -- there were six in the moxifloxacin

7   treated arm and two in the other. So, I guess the

8   calculation is a little bit complicated to perform,

9   but it may just give you some sort of relative idea.

10   DR. RUSKIN: And, I had one other question

11   that related to exclusion criteria. We heard about the

12   fact that patients exposed to Class 1A and Class 3

13   anti-arrhythmic drugs were excluded from the

14   protocols, at least part way through, but I wasn't

15   aware earlier that patients with baseline QT

16   prolongations were excluded. Can you tell us what the

17   cutoff was and when that was implemented?

18   DR. SACKS: That was implemented at the

19   inception of the ECG studies, that was in, I think it

20   was, May, '97 did I say? I'm not sure what the actual

21   baseline was, and we could ask Bayer to supply us with

22   that information.

23   DR. HOLLISTER: Alan Hollister from Bayer.

24   This exclusion was subjects with known congenital QT

25   prolongation. That was the term that was used for

1 exclusion, not baseline prolongation.

2 DR. RUSKIN: S o , was it based on an

3 interval or a clinical diagnosis?

4 DR. HOLLISTER: It was based on a history

5 of known QT prolongation.

6 DR. RUSKIN: Can you tell us how many

7 patients were excluded on that basis?

8 DR. HOLLISTER: Any idea? No.

9 ACTING CHAIRMAN RELLER: Dr. Parsonnet.

10 DR. PARSONNET: The sponsor showed us a

11 number of different ways of looking at QT

12 prolongation, including greater than 60, a change in

13 greater than 60, and 500, greater than 500 absolute

14 QTc, and I was wondering, you presented -- your data

15 looked quite different because you presented, it looks

16 like, just the greater than **500,** whereas, the

17 sponsor's data look most pronounced for the greater

18 than 60 change. And, I was wondering whether you

19 looked at that as well, and why you chose to present

20 us just with the absolute greater than 500.

21 This is not in my area, obviously, so **I'm**

22 not really sure what numbers we should be paying most

23 attention to.

24 DR. SACKS: I can answer that in part. We

25 did look at prolongations. For practical reasons, I

1   was given the prolongations by the Cardiorenal

2   Division, at levels greater than 80 milliseconds, and

3   we thought that that was, perhaps, not the standard

4   comparison as referred to in the CPMP document.

5   But, based on that comparison, we got very

6   similar results to those presented by Bayer.   There

7   were nine patients who developed a greater than 80

8   millisecond prolongation on moxifloxacin out of about

9   559, versus one patient on comparator.

10   DR. PARSONNET: I just have maybe a

11   question for the consultants about, are there certain

12   numbers that we should be paying more attention to

13   than others? What are the significant values for us

14   to really consider?

15   DR. MORGANROTH: Joel Morganroth.   As I

16   said before, I think that the real issue is not that

17   the numbers you are striving for tell you that that's

18   a danger level versus a safe level.   It's really a cut

19   point, an outlier cut point, that suggests that the

20   drug is more likely causing that QTc increase than

21   spontaneous variability. And, when you look at normal

22   variability   data   to   make   that   judgment, 60

23   milliseconds turns out to be very good atr that, 15

24   percent change from baseline tends to be very good for

25   that. Obviously, anything higher than that, which is

1 implied by 500 or greater, would, of course, be almost

2 always, but not always, drug effect versus spontaneous

3 variability, and I think that's the purpose.

4 The issue as to which amount of QTc is

5 sort of dangerous versus not, as we've heard today, I

6 think is not clear because there is no good

7 relationship that's ever been established between

8 degree of QT prolongation and incidence of Torsade.

9 As Dr. Ruskin appropriately pointed out, we've seen

10 cases of Torsade with very minimal QTc prolongation,

11 but most clinicians have seen most of the Torsade with

12 400, 500, 550, 600 milliseconds.

13 And, I think as Dr. Temple pointed out, 20

14 milliseconds or greater as a mean effect would be sort

15 of a number that I'd be very nervous about, where

16 anything in this one to ten range, or one to, I guess,

17 less than 20 range, is unknown in terms of where that

18 risk is in terms of quantitative risk compared to the

19 benefit that you have to judge.

20 DR. RUSKIN: I would agree with that, but

21 I would add one point, and that is that, while it is

22 true that it's important to distinguish spontaneous

23 variability from drug effect, we have the benefit in

24 many of these studies now of a control population.

25 So, it's important to ask what the drug does in

1 relation to the control agents, and if you see a

2 change in distribution in relation to a control

3 population then you are talking about more than just

4 spontaneous variability, you are talking about a

5 difference between two sets of agents, and there

6 appears to be some difference here.

7 What the clinical significance of that is,

8 and how much it actually predicts events, is something

9 that we can't answer, but there does appear to be some

10 difference.

11 ACTING CHAIRMAN RELLER: Dr. Norden.

12 DR. NORDEN: Yes, can I ask Dr. Ruskin a

13 question based on Dr. Sacks' presentation? Do you

14 have any concerns about the difference in the rate of

15 atrial fibrillation in the two populations, which was

16 striking?

17 DR. RUSKIN: I was intrigued by that. I

18 have no idea what the significance of that is. I can

19 tell you, and this is getting very hypothetical, that

20 there are some people who believe in the concept of

21 atrial Torsade and that Class 3 agents, typical Ikr

22 blockers, may have effects on atrial muscle that may

23 predispose them to arrhythmias, perhaps, AF. I am not

24 aware of any clinical data to support that, it's

25 purely hypothesis at this point. But, I was equally

1   intrigued by the observation, I don't know how to

2   explain it.

3   DR. RODVOLD: If I understood all the

4   presentations, most of the data that's on the QT

5   against serum concentrations from Phase I, Phase II,

6   mainly human volunteer type studies, dose ranging

7   studies, was there a population analysis done on PK of

8   serum levels in patients in these studies, and are

9   those serum levels in those patients different than

10   those volunteer data?

11   DR. SACKS: Yes, I'm not aware of any such

12   data on the clinical database and the clinical trials.

13   I don't know if Bayer has any other to offer or not.

14   ACTING CHAIRMAN RELLER: Dr. Platt?

15   DR. PLATT: Both Dr. Morganroth and Dr.

16   Temple have said 20 milliseconds is a number to keep

17   in mind. And, with that thought I wonder if we could

18   see Dr. Sacks' slide No. 12.

19   I appreciate that these data come from

20   normal volunteers, but it seems the data are very

21   consistent with the clinical trial data, and what I

22   understood from the briefing papers is that the steady

23   state concentration is about 4,500.   If that's

24   correct, that suggests that even though there isn't

25   much data, Dr. Ruskin's comment that most of the data

1   we're looking at don't speak about the likely clinical

2   population who would be treated comes to bear because

3   it suggests that at 4,500 the best guess is that the

4   prolongation would be about 20 milliseconds. And, of

5   course, there's only one person who is out at that

6   concentration on this table, but it would also suggest

7   that there might be a substantial fraction who are up

8   above 60 milligrams as prolongation.

9   So, is that a -- my question is, is that

10 a correct interpretation of these data, that most of

11 the data don't speak to the clinical use, but that

12 there's **a** suggestion that 20 milliseconds might be in

13 range?

14   DR. RODVOLD   Can I add to that just one

15 moment before you answer that? Is that slide correct

16 on   the   bottom   statement,   that   mean   serum

17 concentrations for the 400 milligram is 2,165? The

18 briefing document from the FDA says it's 4,500 for

19 steady state, but even single dose in the sponsor's

20 packet says 3.3 or 3.36, and I was wondering how you

21 got 21 up there?

22   DR. SACKS: This was a subpopulation that

23 we analyzed. This was based on a single oral dose,

24 400 milligrams, and it was taken at presumed Cmax,

25 which could have been any time from two to six hours

afterwards. I noticed that in the sponsor's briefing

package the numbers of patients referred to, they were

small, but I can't really make **a** claim for exactly why

those differences occurred.

This is definitely not steady state, **I**

must point that out, this is Cmax. I don't know if

the company has any responses.

DR. HOLLISTER: I think there's always

concern when we are trying to do regressions, and, in

fact, the FDA took us to task for having multiple

points down here at a very low level, or zero level,

and rightfully so, because if you are trying to do a

regression to identify a drug effect, then a zero

concentration should not be included in your

regression line.

So, there may be some of that influence

here. These are, as the slide indicates, just single

dose, and with multiple dose administrations the

concentration is higher. The dearth of points out

here doesn't help us very much in terms of identifying

the relationship. I think the bottom line, though, is

that in the several thousand patients who did receive

steady state concentrations, who got the EKGs at

presumed Cmax, our mean effect **was** six milliseconds.

DR. MORGANROTH: This is Joel Morganroth.

1   In reference to Dr. Platt's prior question

2   about the 20 milliseconds, those comments, and I

3   assume what Dr. Temple meant, he's here and he could

4   speak for himself, but what I meant was, if you look

5   at large Phase III databases in drugs on clinical

6   development, and if you look at electrocardiograms

7   taken and measured properly, if you see a mean change

8   of 20 milliseconds and you look to see what happened

9   to those drugs that reached that level or greater when

10   used clinically, and you find that a lot of them have

11   a lot of incidence of Torsade. I showed you a slide

12   earlier with anti-arrhythmic drugs that had 20 to 60

13   milliseconds in which the prevalence of Torsade was,

14   what, anywhere from one in ten to one in 100, and I

15   think Dr. Temple mentioned a drug that had a 20

16   millisecond, I don't think it was approved in the

17   United States, I'm pretty sure it was not, it was

18   approved in Europe, and it had a lot of Torsade that

19   occurred afterwards in a non-cardiac drug. And so,

20   that's where the number 20 comes from, if you reach a

21   mean of 20 or greater in a big population, you know,

22   that's a long enough number that clinical experience

23   suggests that that might be important in terms of

24   actual   real   Torsade   incidence   in   the   treated

25   population.

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1   And, with moxifloxacin, that database

2   turned out to be six, and I'm not sure -- I don't

3   think it's fair to take normal volunteers and find

4   that at a certain level that some of them had 20

5   milliseconds, because remember the normal variability

6   could be much higher than that, and to make any

7   suggestions that, therefore, that would be a more

8   dangerous drug than if you don't see that, you see a

9   flatter dose response curve.

10   In my experience, the dose -- or let me

11 put it a different way, the concentration in plasma to

12 the QTc effect relationship looks almost like that

13 slide you saw for every drug that I've seen. I mean,

14 there's very poor correlations between plasma

15 concentrations and QTc duration in milliseconds. With

16 dose and QTc, there's some drugs that have a good

17 relationship, like terfenadine.   You have .128

18 milliseconds per milligram of dose, and it's at

19 linear. But, most other drugs it's too scattered to

20 really make even an oral dose to QTc relationship.

21   ACTING CHAIRMAN RELLER: Dr. Murray.

22   DR. MURRAY: Yes. I apologize, because

23 this has probably been asked and answered, but the

24 levels that we have heard about, the blood levels,

25 drug concentrations that we have heard about, are all